4) Any other problems.

Site audit Each site will be surveyed within 6 months after the study commencement. The site audit team nominated by the Steering Committee will survey the sites according to the Site Audit Manual. The audit team will report the results to the Steering Committee, which will review them.

Reporting of adverse events and protection of participants

Definition of adverse events

An adverse event is defined as any unwanted or unintended sign (including laboratory exams), symptom or disease seen in participants of the trial, regardless of the causal relationship with the study intervention.

Reportings according to Pharmaceutical Affairs Act (1950 Law 145)

All the protocol interventions in the current trial are within the approved dosage and administration in Japan and will therefore have to follow the Japanese Pharmaceutical Affairs Act.

Adverse events will be assessed according to the "Adverse Events Manual" which follows the Japanese Ministry of Health, Labour and Welfare's "Manual for rating the severity of side effects by pharmaceutical products," with an amendment to allow more detailed assessment of suicidality according to Columbia Classification Algorithm for Suicide Assessment (C-CASA) [48].

Adverse events will be classified into:

Grade 1: minor side effects
Grade 2: neither major nor minor side effects
Grade 3: major side effects, i.e. side effects that may lead to death or to enduring severe impairment depending on the patient's conditions and circumstances

All grade 3, and unforeseeable grade 2 adverse events shall be reported to the relevant section of the Ministry of Health, Labour and Welfare as well as to the national centre office. Foreseeable adverse events are judged according to the package inserts of respective drugs. Any grade 3 adverse events that occurred within 30 days of the completion of the protocol treatment shall be reported to the Ministry and the national centre office. The reporting shall be done using the attached "Reporting form on safety of pharmaceutical products."

The principal investigator, upon receiving the report, will consult with the trial physician to discuss the course of actions to be taken with regard to the patient in question and also with regard to the study.

Reportings according to the Ethics Guideline for Clinical Research (Ministry of Health, Labour and Welfare, revised in 2008)

When a serious adverse event occurs, the trial physician must take all the necessary and appropriate measures to ensure safety of the participant. He/she must also notify the principal investigator immediately. The principal investigator must notify co-principal investigators at all the regional centres within 24 hours, and report to the head of the clinical research institution (In the pilot study, Director of Nagoya City University Hospital or Director of Kochi Medical School Hospital) through the co-principal investigators. The principal investigator must also notify all the collaborators. The head of the clinical research institution must report to its own IRB and, if it concerns an unforeseeable serious adverse event, must report to the Ministry of Health, Labour and Welfare.

"A serious adverse event" is defined here as "an adverse event that may lead to death or to enduring severe impairment depending on the patient's conditions and circumstances" and will include:

1. Death
   1.1. All deaths regardless of causal relationship with the protocol treatment, if it is a death during the protocol treatment
   1.2. Deaths whose causal relationship with the protocol treatment cannot be denied, if it is a death within 30 days after completion of the protocol treatment.
2. Life-threatening event
3. Event leading to enduring and severe impairment and dysfunction

When treatment is required, the trial physician will provide and/or arrange appropriate treatments including hospital admission.

Foreseeable adverse events according to the package inserts

Sertraline Frequent side effects

Nausea (18.9%), somnolence (15.2%), dry mouth (9.3%), headache (7.8%), diarrhea (6.4%), dizziness (5.0%) etc.

Serious side effects

Serotonin syndrome (unknown frequency), malignant syndrome (unknown frequency), convulsion (unknown frequency), coma (unknown frequency), liver dysfunction (unknown frequency), SIADH (unknown frequency), Lyell syndrome & toxic epidermal necrolysis (unknown frequency), anaphylactoid symptoms (unknown frequency)

Mirtazapine Frequent side effects

Somnolence (50.0%), dry mouth (20.6%), fatigue (15.2%), constipation (12.7%), increased AST/ALT (12.4%)

Serious side effects

Serotonin syndrome (unknown frequency), agranulocytosis/neutropenia (unknown frequency), convulsion (unknown frequency), liver dysfunction/jaundice (unknown frequency), SIADH (unknown frequency)

Stopping Rule For Study

The study will be discontinued by the Steering Committee (or the principal investigator in the case of an emergency) upon advice from the DSMB if any of the following conditions is met.

1) The causal relationship between any of the protocol treatments and serious adverse events including death is established by this study or by any other study.
2) Provision of study drugs becomes impossible for any reason.

Data Management And Publication Policy

Data Management

The data management will be done by the data centre. The electronic data is anonymized in a linkable record, and the participants' names and ID numbers will be recorded only on non-electronic media (e.g. paper notebook) and kept at each trial site.

The central CRC will check the progress of all the entered participants every day by use of the EDC and will contact the site CRC or the trial physician should any doubt arise.

The data centre will perform similar checks and will contact the central CRC should any doubt arise.

Publication Policy

The protocol will be published, with TAF as first author.

The main papers stemming from Steps I, II and III, especially the one from Step II, will be submitted to a high impact journal. The collaborating researcher has the right to be the first author of these papers in order of their number of recruitment. TAF will remain the corresponding author for all the papers. All the trial principal physicians and the trial participating physicians who have entered more than 10 patients will appear as co-author of at least one paper.

Trial principal physicians, trial participating physicians and other members of the Steering Committee, if they do not appear as co-author, will be listed at the end of the article. Such authors may be counted as co-authors in some journals but not in others.

The results shall be reflected in treatment guidelines and systematic reviews.

Study Period

The study period of this trial will be between December 2010 and March 2014, with the patient entry period between December 2010 and September 2013.

The study period of the pilot study will be between December 2010 and March 2012, with the patient entry period between December 2010 and October 2011.

Statistical Analyses

Sample size calculation

Sample size for Step I Assuming an intra-cluster correlation coefficient to be 0.05 [37,38], with alpha error at 0.05 and statistical power at 0.80, to detect a mean difference of 1 point on PHQ9 (SD = 5), i.e. to detect an effect size of 0.2, we need 66 patients at each of 30 sites. The total sample size is therefore 1980.

Sample size for Step II The clinical question for Step II is the main hypothesis of this trial. Previous studies using PHQ9 in the acute phase treatment of major depression have shown that, on average, the PHQ9 scores will drop from 15 (SD = 5) at baseline to 10 (SD = 6) at end of treatment, with a mean change of 5 (SD = 5) [49-51]. We expect a difference of 20% (1 point) in the PHQ9 change scores among the intervention arms and consider this to be a clinically meaningful difference in effect. With alpha error set at 0.05 and statistical power at 0.80, in order to detect a between-group difference of 1 point (SD = 5) in the reduction of PHQ9 scores from baseline, we need 522 per group and 1566 in toto at Step II. Assuming a dropout rate of 20% and a remission rate of 10% at week 3, we need 2175 participants for Step I.

One point difference in the mean change score on PHQ9 corresponds with an effect size of 0.2. This is a small effect according to Cohen's rough rule of thumb for effect size interpretation [52]. However, because the present trial represents comparison among active treatments and because the true effect size of antidepressants over placebo appears to be around 0.3 [53] and the average effect size of all the health interventions examined in the Cochrane Library appears to be between 0.3 and 0.4 [54], we consider this to be a clinically meaningful difference in effectiveness worth detecting in a large clinical trial. As a matter of fact, an effect size of 0.2 will be translated into an NNT of 10 if the control event rate is around 50% (e.g. response as defined usually by 50% or greater reduction in depression severity from baseline) and 20 if the control event rate is around 20% (e.g. remission of depression) [55]. They therefore represent clinically meaningful difference in effect.

The sample size will be revisited after completion of the pilot study.

Sample size for Step III Step III represents continuation treatment for Steps I and II, and will therefore be

examined as exploratory studies. We therefore will not calculate sample size necessary to detect a significant difference. However, we will calculate the obtained statistical power post-hoc.

Sample size for pilot study The pilot study is a feasibility study and needs no sample size calculation. The target sample size is 200. We will perform no statistical analyses looking at the comparison arms at the end of the pilot study, whose participants will therefore be included in the main study unless there is a major change in the study protocol.

Statistical analyses

Primary analyses For Step I, we will compare the sertraline 50 mg/d arm and the sertraline 100 mg/d arm at an individual level. We will test whether the changes in PHQ9 scores at week 1 through week 3 are statistically significantly different between the two arms. Because Step I employs cluster randomization, we will have to take into consideration intra-class correlation coefficients.

For Step II, we will test whether the changes in PHQ9 scores at week 4 through week 9 are statistically significantly different among the sertraline continuation arm, the mirtazapine augmentation arm and the mirtazapine switch arm. The null hypothesis that the changes are not different among the treatment arms will be tested by examining treatment effect parameters in the repeated measures analyses of all the eligible subjects in the ITT analysis. We will use random effects model taking into consideration the Step I randomization and Step II randomization factors. We will examine interaction effect of Step I cluster randomisation. The test will be double-sided. The alpha error is set at 0.05 and statistical power at 0.80. We will impute the missing data and carry out sensitivity analyses as necessary.

Secondary analyses We will perform secondary analyses to supplement our primary analyses and to obtain more elaborate understanding of our clinical questions. The secondary analyses will use models similar to those of the primary analyses. We will calculate relative risks and their 95% confidence intervals for differences in proportions. We will calculate hazard ratios and their 95% confidence intervals for differences in treatment continuation.

Details of the statistical analyses will be laid down in the "Statistical Analysis Protocol", which will be prepared by the statistician in the Steering Committee by the time the analyses will be undertaken.

Interim analyses We will not perform interim analyses to examine the study hypotheses for two reasons. First, we are not expecting a huge effect size for the planned comparisons and second, it is theoretically likely that trials stopped early for benefit may overestimate the true effect size.

However, we will examine the following aspects in order to ascertain the feasibility of the study without revealing the treatment allocation.

1) Number of entered subjects per trial site to calculate the number of trial sites and the time necessary to complete the intended study
2) The intra-cluster correlation coefficient will be calculated in order to make sure that it is not very different from the one assumed in this protocol. We will re-calculate the sample size if necessary.

The analyses for the pilot study will be given in detail in the "Statistical Analysis Plan."

Ethical Aspects

Adherence to the study protocol and study manual

All the researchers participating in this trial will place the participants' safety and human rights above everything else and will adhere by the study protocol and the study manual so long as they do not undermine their safety and human rights.

Regulations to be adhered to

All the researchers participating in this trial will abide by the Declaration of Helsinki and its amendments as well as the Ethics Guideline for Clinical Research (2008 revision, Ministry of Health, Labour and Welfare).

Procedures for informed consent

Before entry into the trial, the trial physician must explain the following items using the written materials and make sure that the participant has understood the contents of the trial well. Written informed consent will only then be obtained from the participant.

1) About clinical trials
2) Objectives of the trial
3) Name and position of the principal trial physician and names of the participating trial physicians
4) Procedures and duration of the trial and what happens after the trial is over
5) Advantages to be expected and disadvantages to be anticipated
6) Other available treatment options
7) The participant can withdraw consent and stop participating in the trial at any time
8) There is no disadvantage if the subject does not participate in the trial or stops participating in the trial.
9) Medical records that are related to this trial will be seen by study personnel of this trial
10) Privacy will be maintained and protected
11) Contact address and method when the participant wants more information about the clinical trial or when he/she feels unwell

12) Compensation insurance for any health hazards
13) Fundings for this trial
14) Others

Protection of privacy

All the researchers and outsourcers of this trial must strictly protect personal information of the participants in adherence with the Ethics Guideline for Clinical Research and the Private Information Protection Law.

Each trial site, each regional centre and the national centre will collect information in anonymized and linkable format. The data centre will not deal with personal information of the participants. The linking information for the participants is strictly managed at each trial site or at the national centre without being computerized, i.e. in paper format.

At week 3, week 9 and week 25, the central rater will administer PHQ9 and FIBSER by telephone while being blind to the participant's allocated treatment. The central CRC will arrange this blinded telephone call by obtaining the participant's name and telephone number from each clinic every time. The central CRC will not keep this privacy information at the national centre office.

Approval by the IRB

This study has been approved by the Ethics Committee of Kyoto University Graduate School of Medicine, the Institutional Review Boards (IRBs) of Nagoya City University Hospital and of Kochi Medical School Hospital.

Each trial site will seek approval of the same protocol if it has its own IRB. If there is no IRB, the trial site will commission its approval to the IRB at Nagoya City University Hospital or at Kochi Medical School Hospital.

Compensation Insurance

All the protocol interventions in the current trial are within the approved dosage and administration in Japan. However, because the trial involves random allocation, we will contract a private health insurance to compensate for health hazards that have arisen due to this trial. The contract will be between Kyoto University and Tokio Marine and Nichido Fire Insurance Company. This insurance will cover only death or grade 1 impairment or grade 2 impairment whose causal relationship with the trial cannot be negated. Grades 3-14 impairments will not be covered by this insurance but will be covered by the National Health Insurance, which therefore can incur some copayment. Because all the protocol interventions are within the approved dosage and administration, any health hazards may be object of the National Rescue Scheme for Side Effects. If there is any negligence on the part of the physician, it may be covered with the doctors' liability insurance.

Study Organization

Steering Committee

The Steering Committee will hold online meetings every two weeks and offline meetings every two months.

Principal investigator:

Toshiaki A. Furukawa, MD, PhD (Kyoto University Graduate School of Medicine/School of Public Health, Department of Health Promotion and Human Beahvior)

Co-principal investigators:

Tatsuo Akechi, MD, PhD, Norio Watanabe, MD, PhD (Nagoya City University Graduate School of Medical Sciences, Department of Psychiatry and Cognitive-Behavioral Medicine)

Shinji Shimodera, MD, PhD (Kochi University Department of Neuropsychiatry)

Mitsuhiko Yamada, MD, PhD, Masatoshi Inagaki, MD, PhD (National Center for Neurology and Psychiatry, Institute of Mental Health)

Trial statistician:

Naohiro Yonemoto, MPH (National Center for Neurology and Psychiatry, Translational Medical Centre)

Data and Safety Monitoring Board: DSMB

DSMB will consist of three professionals in clinical trials and in psychiatry, who are not involved in this trial: Dr Teruhiko Higuchi (Psychiatrist, National Centre for Neurology and Psychiatry), Professor Yoshio Hirayasu (Psychiatrist, Yokohama City University) and Akiko Kada (Biostatistician, National Cerebral and Cardiovascular Center). The purpose of DSMB is to check the data monitoring reports prepared by the data centre and make recommendations, where necessary, to the principal investigator.

Research organization

Figure 3 shows the organizational structure for the pilot study.

Data centre

The data centre will be in charge of collecting and managing information independently from the researchers. The data centre will handle site registration, participant registration and allocation, monitor data entry, manage quality assurance of data, manage quality control of data, prepare monitoring reports, and prepare datasets for statistical analyses.

The data centre will make monitoring reports on the progress of recruitment, progress of data collection and adverse events to the Steering Committee and DSMB.

The data centre will be entrusted a contract research organization to be chosen by public tender bidding.

National centre and Regional centres

The national centre office will be located within Department of Health Promotion and Behavioral Medicine, Kyoto University School of Public Health. It will have a central rater, a CRC and a secretary.

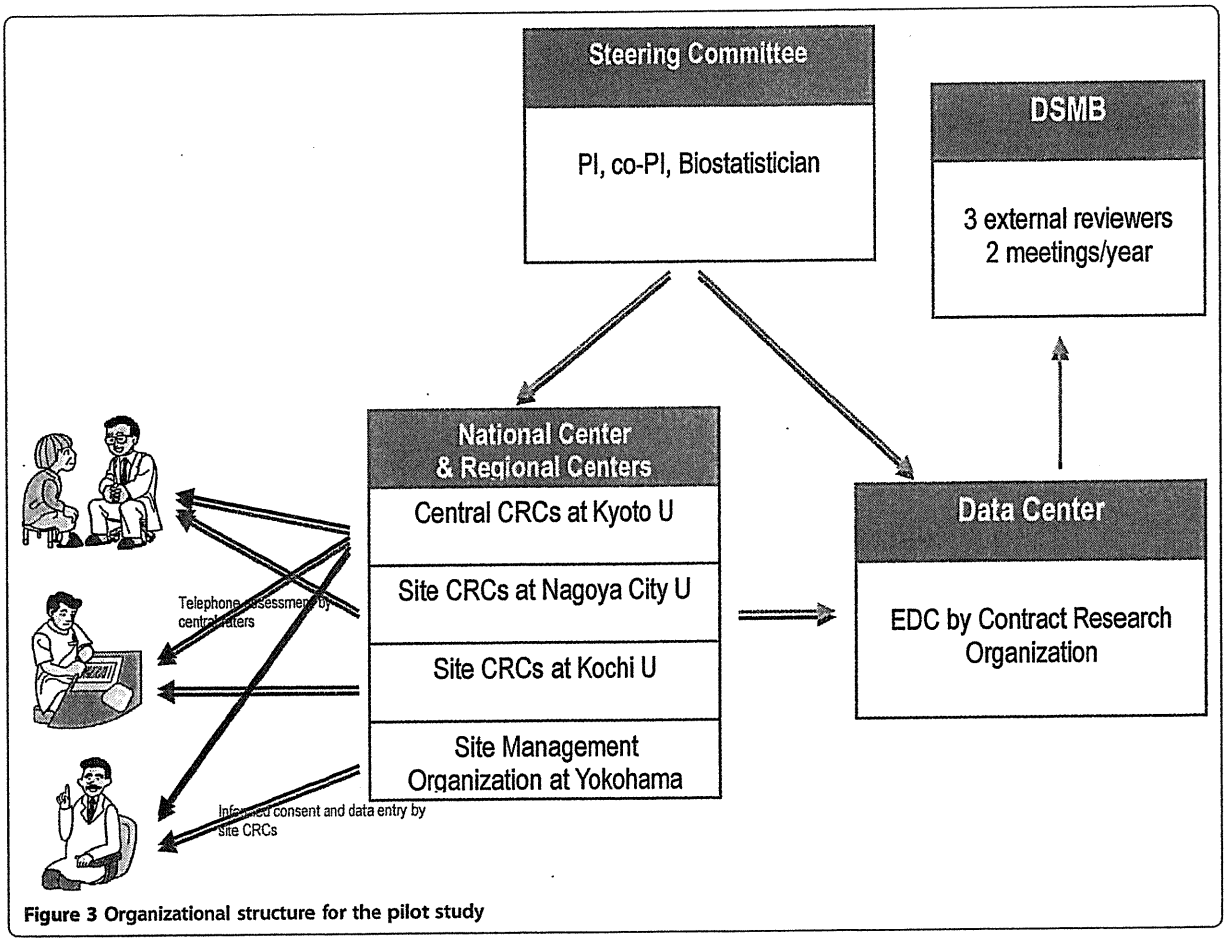

Figure 3 Organizational structure for the pilot study

There will be regional centres at Nagoya City University and Kochi University. There will be site CRCs who will make weekly visits to participating trial sites to assist informed consent procedures and to monitor and enter clinical data.

Discussion

The SUN(^_^)D is an assessor-blinded, parallel-group, mutli-centre randomised controlled trial sequentially comparing active treatment options and combinations currently approved for treatment of depression in Japan.

The prominent characteristics of the SUN(^_^) D include the following.

First, the treatment arms in this trial are based on true clinical uncertainty, because all of them are treatment options currently approved by the regulatory bodies in Japan. In other words, they represent treatment alternatives from which both clinicians and their patients have difficulties choosing at the present moment.

Second, the clinical questions to be examined in this trial pertain to urgent and critical decision points for which the world psychiatric and psychopharmacological research community has hitherto failed to provide guidance or answer to.

Third, the trial will take place mostly in front-line psychiatric facilities such as private practices and departments of psychiatry of general hospitals from all over Japan, where many if not most of the patients with major depression receive their initial treatment. Because Japan does not have the primary care system as represented by the general practitioners in UK, these are the primary care mental health services in Japan and the current trial is thus expected to have maximum external validity with respect to initial treatment of major depression in Japan.

Fourth, several important measures are built in to ensure good internal validity for this pragmatic trial, such as central randomization, blind assessment of symptoms and side effects via telephone and adherence to true intention-to-treat principle through differentiation of discontinuation of protocol treatments and withdrawal from study. Whether we can achieve the last point will depend on whether we can follow up and assess all the patients even when they stop or deviate from the assigned treatments.

As discussed in the Introduction, major depression represents the greatest non-fatal burden of disease for the humankind, with commensurate rise in spending on the antidepressants world-wide. We maintain that this must be accompanied by commensurate increase in evidence base to guide their wise clinical administration. For example, the total annual sales of antidepressants amount to 120 billion yen (1.3 billion US dollars), and we would like to advocate that at least 0.1% of this sum be spent on public-domain pragmatic research of their use for mood and anxiety disorders. Many urgent and critical clinical questions can be answered with this research funds only if the research can be simple and pragmatic enough. We hope that SUN(^_^)D can be a template for such future clinical trials, and that it ultimately can provide good evidence to improve the treatment guidelines for depression in the world.

List of abbreviations

5-HT: 5-hydroxytryptamine; BDI2: Beck Depression Inventory-II; C-CASA: Columbia Classification Algorithm of Suicide Assessment; CRC: Clinical Research Coordinator; CRO: Contract Research Organization; CYP: Cytochrome pigment; DALY: Disability-Adjusted Life Years; DSMB: Data Safety Monitoring Board; EDC: Electronic Data Capturing; FIBSER: Frequency, Intensity, and Burden of Side Effects Rating; MANGA: Meta-Analyses of New Generation Antidepressants; MAO: Monoamine oxidase; NICE: National Institute of Clinical Excellence; NaSSA: Noradrenergic and Specific Serotonergic Antidepressant; NNT: Number needed to treat; PHQ9: Personal Health Questionnaire-9; RCT: Randomized controlled trial; SMO: Site Management Organization; SNRI: Serotonin & Noradrenalin Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression; SUN ☒ D: Strategic Use of New generation antidepressants for Depression.

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Authors' contributions

TAF conceived the study, TAF, MY, MI and NY prepared the original manuscript. TAF, TA, SS, MY, KM, NW, MI and NY participated in the refinement of the protocol. NY is the trial statistician. All authors critically reviewed and approved the final version of the manuscript.

Competing interests

TAF has received honoraria for speaking at CME meetings sponsored by Astellas, Dai-Nippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Kyorin, MSD, Meiji, Otsuka, Pfizer, Shionogi and Yoshitomi. He is on advisory board for Sekisui Chemicals and Takeda Science Foundation. He has received royalties from Igaku-Shoin, Seiwa-Shoten, Nihon Bunka Kagaku-sha and American Psychiatric Publication. TA has received speaking fees and/or research funds from Astellas, Astra-Zeneca, Bristol-Meyers-Squib, Daiichi-Sankyo, Dainippon-Sumitomo, Eisai, GlaxoSmithKline, Janssen, Kyowa-Hakko-Kirin, Lilly, Meiji, Otsuka, Pfizer, Sanofi-Aventis, Shionogi and Yakult. NW has received speaking fees and/or research funds from Dainippon-Sumitomo, GlaxoSmithKline, Lilly, Otsuka, Pfizer, Asahi-Kasei and Shering-Plough. SS has received speaking fees and/or research funds from Astellas, Dainippon-Sumitomo, GlaxoSmithKline, Janssen, Lilly, Otsuka, Pfizer, Shering-Plough, Shionogi and Yoshitomi. MY and NY have no conflicts of interest to declare. NY received royalties from Seiwa-Shoten. MI has received a speaking fee from Lilly. KM has received speaking fees from Astellas, Dainippon-Sumitomo, GlaxoSmithKline, Janssen, Lilly, Meiji, Otsuka, Pfizer and Shering-Plough.

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Short Communication

Serum Brain-derived Neurotrophic Factor and Antidepressant-naive Major Depression After Lung Cancer Diagnosis

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Previous studies have reported the existence of an association between brain-derived neurotrophic factor and major depression. However, the possible role of brain-derived neurotrophic factor in the pathophysiology of major depression after cancer diagnosis has not yet been investigated. Subjects were collected using the Lung Cancer Database project. Using the cut-off scores on the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D), 81 subjects with depression (HADS-D $\geq$ 10) and 81 subjects without depression (HADS-D $<$ 5) were selected. The two groups were matched for age, sex, clinical stage and performance status. The serum brain-derived neurotrophic factor levels were measured using an enzyme-linked immunosorbent assay method. The serum brain-derived neurotrophic factor levels were not statistically different between the subjects in the depression group [29.1 (13.6) ng/ml; mean (SD)] and the non-depression group [31.4 (10.6) ng/ml] ($P = 0.22$). In a stratified analysis by gender, however, the mean serum brain-derived neurotrophic factor level in the depression group tended to be lower than that in the non-depression group among women ($n = 24$ pairs, $P = 0.06$). Major depression after cancer diagnosis is not associated with serum brain-derived neurotrophic factor levels.

Key words: major depression – BDNF – lung cancer – cancer diagnosis – stressful event

INTRODUCTION

Cancer is a common and worldwide fatal disease. Learning about the diagnosis of cancer is an extremely stressful life event, and major depression is common among patients with cancer (1). Stressful events are usually considered as strong risk factors for major depression (2). Therefore, the high

prevalence of major depression among cancer patients may be attributable to cancer-specific stressful events (3). However, the pathway by which stressful events lead to major depression among cancer patients has not yet been elucidated.

Recently, brain-derived neurotrophic factor (BDNF) has been recognized as an important factor in the pathophysiology of stress-related mental disorders, particularly major depression (4). In animal studies, the relationships between the stress and decreased expression of BDNF mRNA in the hippocampus and neocortex of rats (5,6), and increased synthesis of BDNF induced by interventions like depression treatments (7,8) were suggested. Patients with major depression had lower levels of serum BDNF than healthy controls (9–11), and the levels of serum BDNF changed to be normal after treatment for depression (9,11). However, with no such studies in the oncologic setting, we preliminarily planed to examine the difference in serum BDNF levels between subjects with and without antidepressant-naive major depression after being diagnosed as having lung cancer, which is a stressful life event and was not considered in the previous human studies (9–11). We hypothesized that the serum BDNF levels in the subjects developing major depression after being diagnosed as having lung cancer would be lower than in those without depression. We secondarily performed a stratified analysis by gender, because a previous study showed significantly low serum BDNF levels in depressive women, but not in depressive men (11).

PATIENTS AND METHODS

Study Design and Subjects

The present study used secondary samples from our previous study (12) on the Lung Cancer Database project (13). The project was a prospective cohort study to investigate the pathogenesis of and the development of new therapy for lung cancer. The project and the present study were approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center, Japan. All participants provided their written informed consent prior to enrollment.

The details of the inclusion and exclusion criteria of the present study were described in our previous report (12). In concise, patients newly diagnosed as having primary lung cancer were included, and patients with cognitive impairment, past or current histories of mental disorders, and brain neoplasms or brain metastasis were excluded. To remove the influence of severe physical status, patients with a performance status (PS) of 2 or higher were also excluded (PS was defined by Eastern Cooperative Oncology Group).

Assessment of Depression

Self-reported questionnaires, including the Hospital Anxiety and Depression Scale (HADS) (14), were completed during the waiting period prior to admission. The HADS consists of seven-item anxiety and seven-item depression subscales and is used to assess anxiety and depressive symptoms during the preceding week. The Japanese version of the depression subscale of the HADS (HADS-D) has two cut-off points that yield a good sensitivity and specificity for depression screening (10 out of 11; 82.4 and 95.1%, major depression only, 4 out of 5; 91.5 and 58.0%, adjustment disorder and major depression, respectively) (15). In this study, 'depression' was defined based on HADS-D scores without usual procedure such as the Structured Clinical Interview for DSM-IV.

Selection of Depression and Non-depression Groups

Subjects were selected according to the method used in our previous study (12), as follows: (i) all eligible subjects were classified into three groups according to the two cut-off points (10 out of 11 and 4 out of 5) for HADS-D; (ii) the number of subjects in the high-score group (>10) was used as the number of cases with major depression; (iii) the same number of controls in the low-score group (<5) was selected from the eligible subjects so that the two groups were matched for age, sex, PS (0 or 1) and clinical stage as assessed by the TNM classification (Ia–IIIa or IIIb–IV). To compare major depression with non-depression, the cases with high HADS-D scores (>10) were enrolled in the 'depression group', and the cases with low scores (<5) were included in the 'non-depression group'.

Measurement of Serum BDNF

Following an overnight fast, blood samples were collected by registered nurses in the morning (7–9 AM), a few days after admission. After storing the samples for about 2 h at 4°C, the serum was separated by centrifugation (1870*g*, 10 min) and stored at −80°C until further assay. The samples were thawed to 4°C and the serum BDNF levels were measured using an enzyme-linked immunosorbent assay kit (Promega, Madison, WI, USA) (9). The absorbance of samples at 450 nm was measured using an Emax automated microplate reader (Molecular Device, Tokyo, Japan).

Assessment of Demographical and Medical Backgrounds

Information regarding clinical, demographic and social factors were collected from the database and the patients' medical charts (13). These data consisted of sex, age, clinical staging as assessed by the TNM classification, PS, pathologic type of the lung cancer, educational level (longer/not longer than 9 years), smoking status, alcohol consumption status, presence/absence of breathlessness and pain, number of platelets and body mass index.

Statistical Analysis

To analyze the background factors, differences in continuous or categorical variables were analyzed by analysis of variance (ANOVA) and the χ^2 test, respectively.

As the primary analysis, the serum BDNF level was analyzed by ANOVA and analysis of covariance (ANCOVA). Background variables that were statistically significantly different between the two groups were examined as independent variables, with the serum BDNF level as the dependent variable, using the Spearman rank correlation coefficient (for continuous variables) or ANOVA (for categorical variables). Only factors that were related to both the background and the BDNF levels were used as covariates in the ANCOVA. As a secondary analysis, stratified analyses according to sex were also performed. All tests were two-tailed, with P values <0.05 indicating statistical significance. The statistical analyses were performed using the statistical software package SPSS for Windows (Version 16.0J, SPSS Japan Institute Inc.)

RESULTS

Participants

During the period of the study, 30 patients refused to participate, while 829 patients provided blood samples and completed self-reported questionnaires. Based on the inclusion/exclusion criteria, 717 patients were found to be eligible for enrollment in the present study (13). Of the 717 subjects, 81 had high HADS-D scores (>10) and were selected as the subjects of the depression group. Of the remaining 319 subjects with HADS-D scores of 4 or under, 81 subjects matched for age and sex were enrolled as controls in the non-depression group.

Group Backgrounds

Table 1 shows the background characteristics of the two groups, including some data that were reported in our previous study (12). The depression group contained more subjects with breathlessness than the non-depression group. Except for the breathlessness, no other variable differed significantly between the groups. The mean and standard deviation in the interval between completion of the HADS questionnaire and the blood sampling in all the subjects were 3.6 and 5.0 days, respectively; these values were similar for both groups [depression group; 3.9 (5.0) days; mean (SD), non-depression group; 3.8 (5.9) days] ($F = 0.04$, $P = 0.85$). The serum BDNF levels showed no significant differences between the subjects with breathlessness [$n = 82$; 28.7 (11.3) ng/ml; mean (SD)] and those without breathlessness [$n = 78$; 31.9 (13.0) ng/ml] ($F = 2.66$, $P = 0.11$).

Table 1. Background of all subjects ($n = 162$)

	Depression	Non-depression	χ^2 or F[a]	P-value
HADS-D (score)	11–21	0–4		
Number	81	81		
Sex (male)	57 (70%)	57 (70%)	0.0	1.00
Age (y.o.)	65.1 ± 8.3	65.0 ± 8.3	0.003[a]	0.96
Performance Status (0/1)[b]	23/58	23/58	0.0	1.00
Clinical stage				
Ia–IIIa[c]	34 (42%)	34 (42%)	0.0	1.00
IIIb–IV[c]	47 (58%)	47 (58%)		
Educational level (>9 years)	52 (64%)	56 (69%)	0.46	0.50
Alcohol (>45 g/day)	14 (17%)	12 (15%)	0.38	0.54
Current smoker	33 (41%)	30 (37%)	0.23	0.63
Pathology				
Adenocarcinoma	42	45	1.49	0.83
Squamous cell	19	20		
Small cell	6	7		
Large cell	8	6		
Other	6	3		
Breathlessness (presence)	49 (60%)	33 (41%)	5.61	0.018
Pain (presence)	28 (35%)	31 (38%)	0.19	0.67
Body mass index (kg/m^2)	22.0 ± 3.5	22.1 ± 3.2	0.06[a]	0.80
Platelet ($10^4 \times \mu l$)	27.7 ± 9.3	28.3 ± 9.4	0.20[a]	0.66

Age, body mass index and platelet: mean ± SD. PS: number. Others: number and percentage.
[a]F-value.
[b]Defined by Eastern Cooperative Oncology Groups.
[c]Defined by TNM Classification, International Union Against Cancer.

Serum BDNF Levels in the Two Groups

Figure 1 illustrates the absence of any significant difference in the serum BDNF levels between the depression group and the non-depression group (ANOVA). The serum BDNF levels were normally distributed. Since no covariates were detected as statistically significant variables in the background analyses, ANCOVA was not performed. In the stratified analyses by gender, no significant differences were seen between the two groups among the men. The mean serum BDNF level was lower in the women with depression than in the women without depression, but the difference was not statistically significant.

DISCUSSION

This is the first study, to the best of our knowledge, conducted to investigate the association between serum BDNF levels and major depression in the oncologic setting.

Unlike in previous studies (9–11), the serum BDNF levels were not lower in the subjects with major depression in the

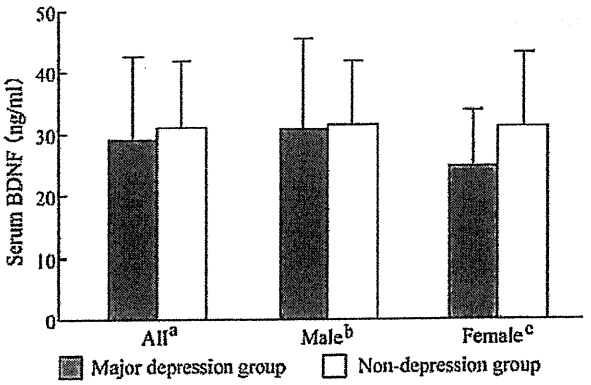

Figure 1. Serum levels of brain-derived neurotrophic factor (BDNF) in the depression group and in the non-depression group. [a]The primary analysis showed the absence of any statistically significant differences in the serum BDNF levels between the subjects in the depression group [$n = 81$; 29.1 (13.6) ng/ml; mean (SD)] and the non-depression group [$n = 81$; 31.4 (10.6) ng/ml] ($F = 1.53$, $P = 0.22$). [b]A stratified analysis by gender showed the absence of any statistically significant difference in the levels between the depression group [$n = 57$; 30.9 (14.8) ng/ml; mean (SD)] and the non-depression group [$n = 57$; 31.8 (10.2) ng/ml] ($F = 0.13$, $P = 0.72$) among men. [c]A stratified analysis by gender also showed the absence of any statistically significant difference between the depression group [$n = 24$; 24.7 (9.1) ng/ml; mean (SD)] and the non-depression group [$n = 24$; 30.7 (11.7) ng/ml] ($F = 3.87$, $P = 0.06$) among women.

present study. The lack of difference in the serum BDNF in our study might be related to the characteristics of depression in oncologic settings, which tends to be reactive to stressful event, mild and of short duration (3,16). In a previous study in which psychiatric patients without cancer were examined, the mean durations of depressive episodes were 0.78 years (9). Of the 81 cancer patients with major depression in the present study, 60 completed the HADS questionnaire within 1 month of the disclosure of their lung cancer diagnosis. None of the subjects in the major depression group visited the clinical psychiatric service or received antidepressants before or after their enrollment in this study. Although the duration of major depression was not directly assessed, the subjects with major depression in the present study might have had mild depression of short duration that remitted by themselves without antidepressants. The associations between peripheral BDNF and severity or duration of depressive episode were not concluded (17). Further study may be needed.

In the present study, depression was defined using the cut-off scores of the HADS-D and not by a structured psychiatric interview (such as the Structured Clinical Interview for DSM-IV). The one-point assessment of HADS-D might not always indicate a major depressive episode defined by DSM-IV; this could be a reason why the present result differ from previous studies' (9–11).

Although the P value did not reach statistical significance, our secondary analysis showed that women with major depression tended to have a lower serum BDNF level than women without depression. This result may support the result of a previous study suggesting an important role of reduced serum BDNF in depressive women, but not in men (11). Other studies reported an association between BDNF and the menstrual cycles in humans (18) and sex hormones in animals (19). Further studies examining these factors may be useful for elucidating the association between BDNF and major depression.

This study had the following limitations: (i) subjects with severe depression might have been excluded from this study because subjects with poor physical activity and cognitive impairment were ineligible and 30 subjects refused to participate in this study. (ii) Although peripheral BDNF was suggested to partly reflect the BDNF levels in cerebral spinal fluids (18,20), serum BDNF was mainly stored in platelets. Relation of serum BDNF levels to BDNF in hippocampus was uncertain. Further studies may be needed to reach definitive conclusions.

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Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Reliability and validity of the Japanese version of the Agitated Behaviour in Dementia Scale in Alzheimer's disease: three dimensions of agitated behaviour in dementia

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Key words: *caregivers, dementia, physically agitated behaviour, psychosis, verbally agitated behaviour.*

Abstract

Background: Agitation in dementia seriously affects not only patients' quality of life (QOL), but also caregivers' QOL. Thus, an appropriate assessment of agitated behaviour in dementia is needed for clinical management. We developed the Japanese version of the Agitated Behaviour in Dementia scale (ABID), examined its reliability and validity, and carried out its factor analysis to elucidate its factor structure.

Methods: The Japanese version of the ABID was given caregivers of 149 Japanese patients with Alzheimer's disease (AD). The internal-consistency, test–retest reliability and concurrent validity of the Japanese version of the ABID were then examined. A factor analysis was used to examine the agitated behavioural dimensions underlying ABID.

Results: The Japanese version of the ABID showed an excellent internal reliability for both frequency ratings (Cronbach's $\alpha = 0.89$) and reaction ratings (Cronbach's $\alpha = 0.92$), and an excellent test–retest reliability for both frequency ratings and reaction ratings. The total score for the frequency ratings of the ABID was significantly associated with the Cohen-Mansfield Agitation Inventory (CMAI), and the total score for the reaction ratings of the ABID was significantly associated with the Zarit Burden Interview. The factor analysis showed three subtypes: physically agitated behaviour, verbally agitated behaviour and psychosis symptoms.

Conclusions: The Japanese version of the ABID promises to be useful for assessing agitated behaviour in patients with AD. Importantly, understanding these subtypes of agitated behaviour might have implications for individualized treatment plans.

INTRODUCTION

Among the various neuropsychiatric symptoms of dementia, agitation is the most distressing manifestation. Agitated behaviours include a wide variety of behaviours, such as making noises, screaming and hurting others. Cohen-Mansfield[1] defined agitation as 'inappropriate verbal, vocal, or motor activity that is not judged by an outside observer to result directly from the needs or confusion of the individual.' Agitated behaviours are common among patients with Alzheimer's disease (AD), dementia with Lewy bodies and frontotemporal dementia.[2] The prevalence of agitation increases with the severity of dementia,[3] resulting in serious daily functional impairment, as agitated behaviours are a complex phenomenon affected by interactions among cognitive impairment, pain, mental discomfort and environmental factors, such as the need for social contact and overstimulation.[1]

Thus, the presence of agitated behaviour might adversely affect not only the patients' quality of life (QOL) but also the caregivers' QOL.

However, the reported prevalence of agitation in patients with dementia is inconsistent. Some studies[2] have suggested a low prevalence of agitation among AD patients with dementia (20–30%); these studies used a multisymptom rating scale, such as the Neuropsychiatric Inventory (NPI).[4] Other studies[5,6] have reported a high prevalence of agitation among AD patients with dementia (60–90%); these studies used an instrument specific for agitated behaviours in dementia, such as the Cohen-Mansfield Agitation Inventory (CMAI).[7] These differences in estimates might arise from not only the lack of a uniform definition for agitation, but also the use of different measurements for assessing agitation and the variety of patient settings (e.g. community residents, nursing homes and outpatient clinics). Cohen-Mansfield suggested that agitation in dementia is manifested in a wide variety of verbal and physical behaviours.[1] More importantly, agitated behaviours in dementia might occur without psychosis (delusions, hallucinations).

Agitated behaviours are problematic in that they can cause severe distress to the caregivers of dementia patients. For the best management of agitation, both a careful and detailed assessment of agitated behaviours and the distress experienced by caregivers in response to the patient's agitated behaviour symptoms are clinically important. Thus, a need exists for the appropriate assessment of agitated behaviour in dementia. The CMAI is the most widely known instrument for measuring agitation in dementia and has been regarded as a useful tool for assessments in clinical trials.[8] The original 29 items of the CMAI were devised to assess agitation among nursing home residents.[7] Later, a revised and expanded version of the CMAI that included 36 items was developed as a community form to assess agitation among community-residing persons.[9] Rabinowitz *et al.* supported the construct validity of the CMAI in large samples with dementia by showing the robustness of the factor structure that emerged on the CMAI across countries.[10] Cohen-Mansfield proposed that agitated behaviours can be classified into several subtypes: verbally non-aggressive, verbally aggressive, physically non-aggressive and physically aggressive.[1]

Another assessment with a specific focus on agitation has also been developed. The Agitated Behaviour in Dementia scale (ABID), originally devised by Logsdon *et al.*,[11] is a useful assessment that utilizes a caregiver-based rating scale. The items in the ABID were derived from clinical experience and other behaviour assessments, such as the CMAI. Thus, a strong correlation between the ABID and the CMAI has been reported.[11] The ABID is believed to have several advantages for detecting and quantifying agitation using agitation-specific rating scales. First, the ABID uses a 16-item scale to assess a wide range of behaviours associated with agitation during the 2 weeks preceding the interview in community-residing patients with mild to moderate levels of dementia. Second, the ABID has the advantage of being able to assess not only the frequency of agitated behaviours, but also the caregivers' reactions to each behavioral problem in patients with mild to moderate dementia. Thus, the ABID provides the possibility of assessing two important outcomes – the frequency of agitation and the caregiver's level of distress in response to the dementia of outpatients. Third, the internal consistency reliability of the ABID has been reported to be excellent (alpha coefficient 0.70).[11] Also, the test–retest reliability of the ABID frequency and the reaction ratings have been reported to have a good external reliability, with correlation coefficients (ICC) of 0.73 and 0.60, respectively.[11] The validity of the ABID has been confirmed.[11] Furthermore, Teri *et al.* suggested that the ABID is an appropriate assessment for evaluating the efficacy of clinical non-pharmacological interventions for agitation in dementia patients.[12] Last, this scale is simple and easy to administer, requiring less than 20 min to complete.

In Japan, although the reliability and the validity of the CMAI have already been established, only the original 29 items of the CMAI for nursing home residents have been published.[13]

The ABID has several clinical advantages over the CMAI for the assessment of dementia in patients with agitated behaviours. First, the ABID might be an appropriate assessment for community-dwelling subjects with mild to moderate levels of dementia.[11] In contrast, the CMAI might be more appropriate for more severely disturbed nursing home residents. Even the community version of the CMAI, which contains 36 items, could not detect any significant differences in terms of the agitation level among AD patients with mild to moderate levels.[8] Second, the

CMAI measures only the frequency of agitated behaviours over the preceding 2 weeks. However, the ABID has caregiver reaction scales in addition to frequency scores. In addition, while the frequencies of observable agitated behaviours over the preceding 2 weeks are rated on the CMAI, the ABID assesses the observable agitated behaviours for each of the preceding 2 weeks and sums the results for a total frequency score.[8,9,11] Thus, the ABID can provide weekly changes in agitated behaviours during the previous 2 weeks in response to clinical interventions, such as clinical non-pharmacological interventions for agitation in dementia patients. Third, psychosis symptoms (delusions, hallucinations) are related to agitated behaviours.[2,14] However, the CMAI did not include any items with psychotic symptoms. In contrast, the ABID includes items related to psychosis (delusions, hallucinations). Thus, for the appropriate assessment of agitated behaviour in dementia, we decided to develop a Japanese version of the ABID for community-residing patients with mild to moderate levels of dementia. Furthermore, we are unaware of any published data regarding the factor structure of the ABID in AD patients. Thus, first, we developed a Japanese version of the ABID using back-translation and ascertained both its reliability and validity. Next, we examined the factor structure of the Japanese version of the ABID among a large sample of AD patients. We hypothesized that different behaviour subtypes (e.g. verbally agitated behaviour and physically agitated behaviour) might underlie the agitation assessed using the ABID, similar to the classification of agitation into several subtypes proposed by Cohen-Mansfield.[1,15]

METHODS

Participants

A total of 169 consecutive Japanese patients with AD who attended Nagoya City Universal Hospital and Yagoto Hospital in Nagoya, Japan, as outpatients between September 2003 and August 2004 were recruited for the present study.

The diagnostic evaluation included a complete history and physical examination, routine blood tests, either a magnetic resonance imaging (MRI) or a computed tomography (CT) scan of the brain, and neuropsychological testing. The study inclusion criteria consisted of (i) a diagnosis of probable AD according to the National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria;[16] (ii) very mild to moderate functional severity (grade 0.5, 1 or 2 on the clinical dementia rating [CDR[17]]); (iii) no history of antipsychotic or antidepressant medication, as these medications can affect the neuropsychiatric symptoms of AD patients; and (iv) residence with a caregiver in a community dwelling. Patients were excluded if (i) other neurological diseases were present; (ii) the patient had a previous history of mental illness or substance abuse before the onset of dementia; (iii) either an MRI or a CT scan showed focal brain lesions; or (iv) reliable informed consent could not be obtained from the patient and/or his/her relatives.

In the present study, AD patients with severe cognitive impairment (grade 3 on the CDR) were not enrolled, because the ABID is most appropriate for assessing observed agitated behaviours in patients with mild to moderate levels of dementia.[11]

Of the 169 patients originally screened, 20 AD patients were excluded from the analysis, because these patients did not meet the inclusion criteria.

The study protocol was approved by the Ethics Review Committee of Nagoya City University Graduate School of Medical Sciences. After the purpose of the study was explained, written informed consent was obtained from each AD patient and, when necessary, from his/her caregivers.

Translation of ABID

The Agitated Behaviour in Dementia Scale (ABID) was developed by Logsdon *et al.*[11] It consists of a 16-item questionnaire seeking responses from caregivers about the common agitated behaviours in dementia patients. With the original authors' permission (R.G. Logsdon and L. Teri), we translated the original English version into Japanese. We followed the standard back-translation procedure to ascertain the semantic equivalence of the Japanese version with the original English version. The back-translated version was examined by Logsdon to point out possible discrepancies. We repeated this process until Logsdon agreed that the original and back-translated versions matched closely.

Procedure

The Japanese version of the ABID was given to all the caregivers by a well-trained psychiatrist. In accor-

dance with the procedure recommended for the original ABID, described by Logsdon *et al.*,[11] the caregivers completed the questionnaire while visiting the outpatient clinic and received minimal assistance from the interviewer.

The ABID includes items that have been identified by Logsdon *et al.*[11] as most problematic in individuals with dementia, and that can be observed and described objectively. The caregivers first rated each behaviour according to the frequency of occurrence during each of the 2 weeks immediately before the assessment on a scale of 0–3 (0: did not occur during the week; 1: occurred once to twice during the week; 2: occurred three to six times during the week; 3: occurred daily or more often). The two weekly scores for each item were then added together, and the resulting item scores ranged from 0 to 6. The item scores were summed to obtain the total score, with possible scores ranging from 0 to 96. Then, the caregivers rated their own reactions to each problem behaviour on a scale of 0–4 (0: not upsetting; 4: extremely upsetting). The caregiver's reactions were rated once for each item and then summed. The total reaction scores had a possible range of 0–64.

At the time of the administration of the ABID, the following tests were also carried out.

1 The Cohen-Mansfield Agitation Inventory (CMAI):[15] This test was originally developed to measure agitation in nursing home residents It consists of 29 observable agitated behaviours rated using a 7-point Likert-type scale according to the frequency of occurrence during the prior 2 weeks (0: never occurred; 7: occurred several times per hour). The reliability and validity of the CMAI have been established by Finkel *et al.*[7] The revised and expanded version of the CMAI, including 36 items, has been developed as a community form to assess agitation among community-residing persons and has been used for senior day center participants.[9] Homma *et al.* confirmed the reliability and validity of the original 29 items of the CMAI in nursing home residents.[13]
2 The Zarit Burden Interview (ZBI):[18] This test consists of 22 items rated using a 5-point Likert scale (never = 0, nearly always = 4) aimed to assess caregiver burden. The total burden was obtained by adding the scores for all the items with a range of 0–88, with higher scores showing a greater burden. The reliability and the validity of the Japanese version of the test battery have been confirmed.[3]
3 Mini-Mental State Examination (MMSE).[19]

Data analysis

We used SPSS 11.0J software for Windows for the statistical analysis.

Reliability

The reliability of this scale was assessed in two ways. First, the test–retest reliability was assessed in 70 caregivers of AD patients at an interval of 1 month after the initial evaluation. The 70 AD patients had not taken any antipsychotic medications not only before the first assessment, but also during the 1-month interval. The test–retest reliability was estimated using analysis of variance intraclass correlation coefficients (ANOVA ICC). In general, an ANOVA ICC above 0.70 shows a good reliability. Second, the internal consistency of the scale was estimated using Cronbach's alpha coefficients (n = 149). A Cronbach's alpha coefficient above 0.70 is indicative of a good internal consistency.

Validity

The concurrent validity of the Japanese version of the ABID was verified by examining the correlation between the ABID frequency ratings and the CMAI, and the correlation between the ABID reaction ratings and the ZBI. The alpha level was set at 0.01.

Factor analysis

A principal component factor analysis using varimax rotation was carried out on the 16 items for both the frequency rating and the reaction rating of the ABID. 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.

RESULTS

Demographic and clinical characteristics

Table 1 shows the mean scores and standard deviations of the clinical and demographic characteristics of both the AD patients and their caregivers. Among the caregivers (n = 149), 73.8% were spouses (n = 110), 19.4% were daughters-in-law (n = 29) and 6.7% were adult children (n = 10). In Japan, the prevalence of AD is reportedly higher in women than in men.[2] In the present study, we also observed a predominance of women (n = 90) among the AD patients. Conse-

quently, male spouses were the main caregivers. Thus, in the present study, the percentage of male caregivers was higher than that of female caregivers.

Table 2 shows the mean of each item according to the ABID frequency and reaction ratings.

Reliability

The test–retest reliability (n = 70) of the ABID frequency and reaction ratings after 1 month showed an excellent external reliability, with a correlation coefficient (ICC) of 0.85 (95% CI = 0.75–0.96) and 0.89 (95% CI = 0.82–0.93), respectively. The alpha coefficients for the ABID frequency and reaction ratings (n = 149) were 0.89 (95% CI = 0.87–0.92) and 0.92 (95% CI = 0.90–0.94), respectively. These scores showed an excellent internal consistency for the total scores.

Table 1 Demographic data of Alzheimer's disease patients and their caregivers

	AD patients Mean ± SD (n = 149)	Caregivers Mean ± SD (n = 149)
Sex (males/females)	59/90	87/62
Age (years)	73.4 ± 8.3	62.6 ± 10.2
Education (years)	9.7 ± 0.8	10.4 ± 2.8
Dementia history		
Duration of illness (years)	3.1 ± 1.1	NA
MMSE	18.9 ± 3.7	28.9 ± 1.7
ABID questionnaire		
Frequency ratings	25.1 ± 18.2	NA
Reaction ratings	19.9 ± 15.3	NA

ABID, Agitated Behaviour in Dementia Scale; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination.

Concurrent validity

The frequency ratings on the ABID were positively correlated with the total CMAI scores (r = 0.86, 95% CI = 0.72–0.91, $P < 0.001$). Similarly, the caregiver reaction ratings on the ABID were positively correlated with the total ZBI scores (r = 0.696, 95% CI = 0.58–0.78, $P < 0.001$). Both the frequency ratings and the reaction ratings were significantly correlated with the total MMSE score (r = –0.82, 95% CI = –0.84 to –0.78, $P < 0.001$, r = –0.83, 95% CI= –0.85 to –0.76, $P < 0.001$) and the duration of illness (r = 0.573, 95% CI = 0.43–0.64, $P < 0.001$, r = 0.573, 95% CI = 0.45–0.68, $P < 0.001$). However, even after controlling for the MMSE score and the duration of illness, the partial correlation between the frequency ratings on the ABID and the total CMAI scores remained significant. Also, after controlling for the MMSE and the duration of illness, the partial correlation between the caregiver reaction ratings on the ABID and the total ZBI scores remained significant.

Factor analysis

An exploratory principal component analysis with varimax rotation using eigenvalues >1 reduced the 16 variables to three factors for both the frequency rating

Table 2 Item means of both the Agitated Behaviour in Dementia Scale frequency scores and the Agitated Behaviour in Dementia Scale caregiver reaction scores among 149 Alzheimer's disease patients

Number; Agitated behavioural characters	Frequency ratings Mean ± SD (n = 149)	Reaction ratings Mean ± SD (n = 149)
1 Verbally threatening or aggressive toward others	2.29 ± 2.01	1.77 ± 1.44
2 Physically threatening or aggressive toward others	1.19 ± 1.96	1.05 ± 1.60
3 Harmful to self	0.67 ± 1.40	0.59 ± 1.18
4 Inappropriate screaming or crying out	1.46 ± 1.75	0.66 ± 0.73
5 Destroying property	0.91 ± 1.62	0.80 ± 1.35
6 Refusing to accept appropriate help	2.21 ± 1.75	1.82 ± 1.41
7 Trying to leave (or leaving) home inappropriately	1.44 ± 2.06	1.21 ± 1.60
8 Arguing, irritability or complaining	2.50 ± 1.95	1.89 ± 1.42
9 Socially inappropriate behaviour	1.07 ± 1.51	1.02 ± 1.59
10 Inappropriate sexual behaviour	0.40 ± 1.01	0.36 ± 0.89
11 Restlessness, fidgetiness, inability to sit still	1.05 ± 1.76	1.02 ± 1.59
12 Worrying, anxiety and/or fearfulness	3.49 ± 2.01	2.29 ± 1.37
13 Easily agitated or upset	2.83 ± 2.21	2.13 ± 1.47
14 Waking and getting up at night (other than trip to the bathroom)	1.19 ± 1.52	0.89 ± 1.24
15 Incorrect, distressing beliefs	1.53 ± 2.11	1.11 ± 1.50
16 Seeing, hearing or sensing distressing people or things that are not really present	0.89 ± 1.68	0.62 ± 1.20

ABID, Agitated Behaviour in Dementia Scale.

and the reaction rating of the ABID. The three factors explained 69.6% of the variance in the frequency rating data of the ABID. The three factors also explained 73.1% of the variance in the data of the reaction rating data of the ABID. Visual inspection of the scree plot also supported a three-factor solution. Tables 3 and 4 show the rotated component matrix of the three-factor solution. The first factor in the frequency rating data of the ABID had high loadings on such items as 'physically threatening or aggressive toward others', 'destroying property' and 'restlessness, fidgetiness, inability to sit still'. According to the subtypes of agitated behaviours,[1,5,20] while 'physically threatening or aggressive toward others', 'destroying property', 'harmful to self' and 'inappropriate sexual behaviour' are categorized into physically aggressive behaviour, 'restlessness, fidgetiness, inability to sit still' and 'trying to leave home inappropriately' with high loadings are regarded as physically non-aggressive behaviour. As in the present study, Cohen-Mansfield *et al.* reported that the latter behaviours were the least disruptive, yet were manifested at a very high frequency among various types of agitated behaviours.[5] Therefore, the first factor was termed 'physically agitated behaviour'. The second factor in the frequency rating data of the ABID included most of the items corresponding to verbally agitated behavior, such as 'arguing, irritability, or complaining' and 'refusing to accept appropriate help', as suggested by Cohen-Mansfield *et al.*[5,20] Therefore, we named this factor 'verbally agitated behaviour'. The third factor in the frequency rating data of the ABID mainly contained items representing psychosis symptoms (delusion, hallucination), such as 'seeing, hearing or

Table 3 Factor analysis of the Agitated Behavior in Dementia Scale frequency scores among 149 Alzheimer's disease patients

	Agitated behavioural characteristics	Factor 1	Factor 2	Factor 3
2	Physically threatening or aggressive toward others	**0.944**	0.168	0.033
5	Destroying property	**0.926**	0.107	0.005
11	Restlessness, fidgetiness, inability to sit still	**0.897**	0.194	0.042
3	Harmful to self	**0.860**	−0.013	0.118
7	Trying to leave (or leaving) home inappropriately	**0.836**	0.208	0.164
10	Inappropriate sexual behaviour	**0.715**	0.067	0.053
8	Arguing, irritability or complaining	−0.092	**0.882**	0.186
1	Verbally threatening or aggressive toward others	0.029	**0.840**	0.304
4	Inappropriate screaming or crying out	−0.101	**0.764**	0.440
13	Easily agitated or upset	0.345	**0.740**	0.142
12	Worrying, anxiety and/or fearfulness	0.289	**0.714**	0.037
9	Socially inappropriate behaviour	0.171	**0.696**	0.263
6	Refusing to accept appropriate help	0.381	**0.562**	0.132
16	Seeing, hearing or sensing distressing people or things that are not really present	0.002	0.170	**0.838**
15	Incorrect, distressing beliefs	0.126	0.288	**0.741**
14	Waking and getting up at night (other than trip to the bathroom)	0.148	0.263	**0.511**

ABID, Agitated Behaviour in Dementia Scale, Factor loadings of 0.511 or more are in boldface.

Table 4 Factor analysis of the Agitated Behaviour in Dementia Scale caregiver reaction rating scores among 149 Alzheimer's disease patients

	Agitated Behavioral characteristics	Factor 1	Factor 2	Factor 3
8	Arguing, irritability or complaining	**0.900**	−0.043	0.151
1	Verbally threatening or aggressive toward others	**0.887**	0.122	0.121
4	Inappropriate screaming or crying out	**0.842**	−0.055	0.255
13	Easily agitated or upset	**0.740**	0.436	0.180
12	Worrying, anxiety and/or fearfulness	**0.729**	0.440	0.026
9	Socially inappropriate behaviour	**0.727**	0.247	0.204
6	Refusing to accept appropriate help	**0.636**	0.448	0.126
14	Waking and getting up at night (other than trip to the bathroom)	**0.522**	0.150	0.340
2	Physically threatening or aggressive toward others	0.272	**0.896**	0.035
5	Destroying property	0.168	**0.891**	−0.007
3	Harmful to self	0.003	**0.884**	0.034
11	Restlessness, fidgetiness, inability to sit still	0.270	**0.883**	0.076
7	Trying to leave (or leaving) home inappropriately	0.300	**0.813**	0.153
10	Inappropriate sexual behaviour	−0.009	**0.709**	0.121
16	Seeing, hearing, or sensing distressing people or things that are not really present	0.199	0.032	**0.872**
15	Incorrect, distressing beliefs	0.386	0.166	**0.711**

ABID, Agitated Behaviour in Dementia Scale, Factor loadings of 0.522 or more are in boldface.

sensing distressing people or things that are not really present' and 'incorrect, distressing beliefs'. Therefore, the third factor was interpreted as representing the 'psychosis symptoms'.

Similarly, a factor analysis of the reaction rating data of the ABID (Table 4) showed that the first factor had a high loading on items associated with 'verbally agitated behaviour'. Therefore, we named this factor of the reaction rating of the ABID 'verbally agitated behaviour'. The second factor included items associated with 'physically agitated behaviour', and we named this factor of the reaction rating of the ABID 'physically agitated behaviour'. The third factor contained items associated with 'psychosis symptoms'. Thus, we named this factor of the reaction rating of the ABID 'psychosis symptoms'.

DISCUSSION

The present study shows that the Japanese version of the ABID scale has an excellent internal consistency reliability for the frequency (alpha coefficient 0.89) and the reaction ratings (alpha coefficient 0.92). The Japanese version of the ABID scale also has an excellent test–retest reliability for the frequency (ICC 0.85) and the reaction ratings (ICC 0.89). As mentioned in the introduction, the internal consistency reliability of the ABID (alpha coefficient 0.70) and the test–retest reliability of the ABID frequency and the reaction ratings, with ICC of 0.73 and 0.60, respectively, have been reported by Logston *et al.*[11] Thus, almost similar levels were obtained for both the internal consistency reliability and the test–retest reliability of the Japanese version of the ABID scale. Furthermore, we showed that each score (the frequency and the reaction ratings) had a satisfactory concurrent validity. Three factors underlying the agitated behaviour evaluated using the Japanese version of the ABID were identified: (i) physically agitated behaviour; (ii) verbally agitated behaviour; and (iii) psychosis symptoms. Therefore, the Japanese version of the ABID scale might be useful for assessing agitated behaviour in community-residing AD patients with mild to moderate dementia.

Cohen-Mansfield proposed that agitated behaviours can be divided into two dimensions: (i) aggressive versus non-aggressive; and (ii) verbal versus physical behaviours.[1,15] Thus, agitated behaviours can be classified into four subtypes: (i) aggressive–physical behaviours; (ii) aggressive–verbal behaviours, (iii) non-aggressive–physical behaviours; and (iv) non-aggressive–verbal behaviours. Most previous factor analyses of the CMAI carried out in different countries have supported these dimensions. However, some studies[15,21] have shown that the CMAI consisted of three factors: (i) physically aggressive behaviours; (ii) physically non-aggressive behaviours; and (iii) verbally agitated behaviours. Other three- or four-factor solutions (aggressive behaviour, physically non-aggressive behaviour, verbally agitated behaviour, and hiding or hoarding) of the CMAI have been found.[5,10] Several items in the CMAI belonged to either physically aggressive behaviour or aggressive behaviour. For example, while several items such as hitting, kicking and pushing were included as physically aggressive behaviour in the former studies,[15,21] the latter studies[5,10] included such items as aggressive behaviour. Despite this disagreement, these factor analyses of the CMAI (the original 29 items) have similar clinical features, as either physically aggressive behaviour or aggressive behaviour were loaded on the first factor in all the previous studies. The difference between 'physically aggressive behaviour' and 'aggressive behaviour' might reflect a difference in whether some items, such as screaming, cursing or verbal aggression, within the subtype of verbally aggressive behaviours are loaded onto the first factor.[10]

In line with previous factor analyses of the CMAI, we named the first factor in the ABID frequency scores as 'physically agitated behaviour'. Several items (e.g. 'harmful to self') in this factor corresponded to the agitated behaviours that Cohen-Mansfield described as being physically aggressive.[1] However, two items in the ABID with high loadings, 'restlessness, fidgetiness, inability to sit still' and 'trying to leave home inappropriately', might correspond to physically non-aggressive behaviour, such as 'general restlessness', 'pacing, aimless wandering' and 'trying to get to a different place' in the CMAI. Previous factor analyses of the CMAI have consistently regarded these items as belonging to the 'physically non-aggressive behaviour' factor.[5,10] Logsdon *et al.*[22] has suggested that both wandering and restlessness can cause significant severe problems among the various agitated behaviours, because these behaviours are associated with severe caregiver distress. However, our factor analysis of the caregiver's reaction ratings in the ABID showed that both 'restlessness, fidgetiness, inability to sit still' and 'trying to leave home inappropriately' were included in the same factor that included other items in