Table 4. Repeated measures ANCOVA comparing first-episode schizophrenia and control group in BACS-J *z*-score

	Between-group differences (group effect)			Within-group differences (time effect)			Group × time interaction		
BACS-J[a]	*F*	d.f.	*p*	*F*	d.f.	*p*	*F*	d.f.	*p*
Verbal memory	2.57	1, 27	0.12	2.22	1, 27	0.15	0.96	1, 27	0.34
Digit sequencing task	0.01	1, 27	0.92	0.07	1, 27	0.80	0.85	1, 27	0.37
Token motor task	0.69	1, 27	0.41	1.27	1, 27	0.27	0.08	1, 27	0.78
Category fluency	0.85	1, 27	0.36	0.006	1, 27	0.94	1.13	1, 27	0.30
Letter fluency	2.43	1, 27	0.13	0.34	1, 27	0.57	8.42	1, 27	0.007
Symbol coding	0.73	1, 27	0.40	0.97	1, 27	0.33	0.73	1, 27	0.40
Tower of London	0.51	1, 27	0.48	0.71	1, 27	0.41	0.38	1, 27	0.54

ANCOVA, analysis of covariance; BACS-J, Brief Assessment of Cognition in Schizophrenia—Japanese language version.
[a]Baseline symbol coding task data were used as covariates.

Table 5. Change in scores of secondary measures from baseline to endpoint in first-episode schizophrenia group

	Baseline ($n=20$)	Endpoint ($n=20$)	Statistics		
	Score	Change	*t*	d.f.	*p*
PANSS[a]					
Positive score	23.8 (3.9)	−10.0 (0.5)	7.48	19	<0.001
Negative score	29.5 (6.4)	−9.0 (0.2)	6.06	19	<0.001
General psychopathology score	56.9 (8.1)	−18.0 (0.6)	8.00	19	<0.001
Total score	109.7 (16.0)	−36.6 (2.1)	7.77	19	<0.001
SQLS-J[a]					
Psychosocial conditions score	70.0 (16.5)	−21.4 (7.2)	4.18	19	0.001
Motivation/energy score	65.4 (15.7)	−11.4 (2.0)	3.09	19	0.006
Symptoms/side effects score	41.6 (16.1)	−11.6 (3.3)	2.94	19	0.008
CGI-S[a]	4.3 (0.8)	−1.6 (0.0)	10.1	19	<0.001
DIEPSS[a]	0.0 (0.0)	1.85 (2.5)	−3.29	19	0.004

CGI-S, Clinical Global Impression—Severity scale; DIEPSS, Drug-induced Extrapyramidal Symptoms Scale; PANSS, Positive and Negative Syndrome Scale; SQLS-J, Schizophrenia Quality of Life Scale—Japanese language version.
[a]Values are mean (SD).

Table 6. Change in scores of PANSS from baseline to endpoint in control group

	Baseline ($n=10$)	Endpoint ($n=10$)	Statistics		
	Score	Change	*t*	d.f.	*p*
PANSS[a]					
Positive score	15.4 (3.7)	2.3 (2.6)	−1.19	9	0.263
Negative score	18.2 (5.7)	1.2 (0.1)	−1.53	9	0.161
General psychopathology score	37.3 (10.5)	−2.5 (6.4)	0.65	9	0.535
Total score	70.9 (18.0)	3.8 (5.2)	−0.98	9	0.354

PANSS, Positive and Negative Syndrome Scale.
[a]Values are mean (SD).

significant correlations between changes in the PANSS total and subscale scores and the SQLS-J scores (all $p > 0.05$).

DISCUSSION

To the best of our knowledge, this is the first study that examined the effects of blonanserin on cognitive function in patients with first-episode schizophrenia, with a control group that was also included and retested to examine potential retest effects. There were three main findings in this study. First, treatment with blonanserin was associated with improvement in letter fluency in this group of patients, as revealed by comparison with age-matched and sex-matched chronic patients. Second, clinical symptoms and subjective QOL were significantly improved after 8 weeks of treatment with blonanserin in first-episode schizophrenia. Third,

improvement in letter fluency with blonanserin treatment was positively correlated with improvement in some domains of subjective QOL.

In this study, we used patients with first-episode schizophrenia who were antipsychotic-naïve before initial assessments. It was thus possible to delineate the profile of cognitive deficits early in the disease process and assess the direct impact of medication. Our sample appears to be representative of first-episode schizophrenia patients as it is similar to other first-episode studies in terms of severity of psychopathology scores and profile of cognitive impairments (Hill *et al.*, 2009; Mesholam-Gately *et al.*, 2009).

Effect of blonanserin on cognitive function

In this study, blonanserin improved letter fluency exclusively in the first-episode patients. Although group-by-time interaction was not significant for executive function, as represented by the Tower of London task, a modest effect size (0.62) was observed only for the first-episode subjects, but not the chronic group (0.10).

Previous studies have suggested that performance on letter fluency task is associated with functional activation in the left prefrontal cortex and the left inferior parietal cortex (Gourovitch *et al.*, 2000; Bokat and Goldberg, 2003; Kubota *et al.*, 2005). In addition, several brain imaging studies have reported activation of the prefrontal cortex, particularly the dorsolateral part during the Tower of London task (Morris *et al.*, 1993; Baker *et al.*, 1996; Owen *et al.*, 1996; Dagher *et al.*, 1999; Lazeron *et al.*, 2000). Taken together, blonanserin may improve letter fluency and executive function, which are probably associated with functional activation in the prefrontal cortex in patients with first-episode schizophrenia. This is consistent with a rodent study reporting the ability of blonanserin to enhance dopamine and norepinephrine release in the prefrontal cortex (Ohoyama *et al.*, 2011). In this context, the lack of a beneficial effect on working memory, as has also been observed with clozapine (Hagger *et al.*, 1993), may be due to an inadequate intensity of dopamine surge. Further studies on blonanserin treatment using functional brain imaging may be worthwhile in the future.

The present findings with regard to cognitive domains improved by blonanserin treatment are different from those reported in our previous study in which blonanserin improved verbal memory, attention, and processing speed in patients with chronic schizophrenia (Miyake *et al.*, 2008). These discrepancies may be due to several factors. First, subjects in the two studies differ in terms of baseline demographic and clinical characteristics such as age, illness chronicity, subtype of schizophrenia, and prior exposure to antipsychotic and/or anticholinergic medications (Miyake *et al.*, 2008). Second, there is a difference in the mean dosages of anticholinergics between the two patient groups. In the previous study, the mean doses of anticholinergics (biperiden-equivalent dose) at baseline and endpoint were 2.9 and 1.4 mg/day, respectively. In the current study, anticholinergic medications were used at a minimum. We have recently reported that discontinuation of long-term biperiden use significantly improved attention and processing speed, as measured by BACS-J, in patients with chronic schizophrenia treated with an SGA (Ogino *et al.*, 2011). Thus, the improvements in attention and processing speed observed in our previous study could be, at least in part, attributed to the reduction of concomitant anticholinergics. Third, we used different doses of blonanserin and cognitive batteries between the two studies. In our previous study, the mean doses of blonanserin at baseline and endpoint were 17.4 and 18.0 mg/day, respectively. We speculate that these methodological differences might have affected the results.

To assess retest effects, we included age-matched patients with chronic schizophrenia treated with blonanserin alone as a reference group. By contrast, several recent studies of SGAs on individuals in their first episode of schizophrenia included healthy comparison groups in which patients and healthy individuals were tested serially over equivalent intervals (Fagerlund *et al.*, 2004; Goldberg *et al.*, 2007; Crespo-Facorro *et al.*, 2009; Andersen *et al.*, 2011). Results of these studies suggest that the effects of practice can notably contribute to cognitive score improvements after treatment with SGAs. Recent data collected from a large clinical trial also show that practice effects are not restricted to a first-episode sample but can be observed in middle-aged chronic multi-episode patients (Keefe *et al.*, 2008; Goldberg *et al.*, 2010). In the present study, chronic patient controls did not show cognitive enhancement in any of the BACS-J subtests, suggesting that retest effects (likely practice effects) were absent in this sample. Although repeated measures ANCOVAs suggest that the observed cognitive score changes in letter fluency score in the first-episode group may likely reflect improvement rather than a retest effect, we cannot exclude the possibility that motivation and expectancy of the subjects confounded the results (Velligan *et al.*, 2006; Goldberg *et al.*, 2010). Although we used chronic patients as a control group, the poor changes in cognitive performance by chronic patients relative to first-episode patients might be due to more pronounced illness-related learning deficits or higher

dosing of blonanserin and anticholinergics. Future studies with a longer duration of blonanserin treatment and the inclusion of healthy controls as a comparator group are warranted to further reduce the possibility of practice effect.

The treatment interval in this study was 8 weeks, which is shorter than that used in other trials of SGAs in first-episode patients (Fagerlund *et al.*, 2004; Goldberg *et al.*, 2007; Crespo-Facorro *et al.*, 2009; Andersen *et al.*, 2011). It is possible that the ability of blonanserin to enhance cognitive functioning may have been greater if patients had been re-examined after a longer interval. However, Keefe *et al.* (2007b) suggested that most of the cognitive benefits of SGAs occur in the early phases (6–10 weeks) of treatment and that further benefits over longer periods may be small. Consistent with this notion, we found significant improvements only on the letter fluency task after 6-month treatment with blonanserin in first-episode schizophrenia patients (Miyamoto *et al.*, unpublished results).

Effect of blonanserin on clinical outcomes and subjective quality of life

In the present study, 8-week treatment with blonanserin significantly improved both positive and negative symptoms as well as subjective QOL. The significant effect on psychopathology in first-episode schizophrenia was in line with previous studies in patients with chronic schizophrenia (Murasaki, 2007a, 2007b; Kinoshita, 2008; Miura, 2008; Miyake *et al.*, 2008; Osada *et al.*, 2009; Yang *et al.*, 2010). Although changes in psychopathology and cognitive function were not significantly correlated, improvement in letter fluency showed a significant correlation with improvement on the SQLS-J motivation/energy score. It has been reported that execution of letter fluency is associated with negative symptoms in schizophrenia (Liddle and Morris, 1991; Allen *et al.*, 1993; Mahurin *et al.*, 1998; Howanitz *et al.*, 2000). In addition, some studies have suggested that negative symptoms, such as letter fluency performance, are related to prefrontal cortical activity (Howanitz *et al.*, 2000). The prefrontal cortex has been shown to be an area of dysfunction in never-medicated patients with first-episode schizophrenia (MacDonald *et al.*, 2005; Snitz *et al.*, 2005; van Veelen *et al.*, 2010). Although we could not find a significant relationship between change in letter fluency or executive function and negative symptoms, further studies are required to clarify the influence of blonanserin on the function of prefrontal cortex as well as social and vocational functions.

Effective dosage and safety of blonanserin in first-episode schizophrenia

In this study, the mean (±SD) daily dose of blonanserin at endpoint was 7.2 (±4.0) mg/day for first-episode patients, which was lower than usual doses. In fact, in three non-comparative, long-term trials of blonanserin in patients with chronic schizophrenia conducted in Japan, the average dose of blonanserin was approximately 13 mg/day (Murasaki, 2007b; Kinoshita, 2008; Osada *et al.*, 2009). It has been suggested that patients with first-episode schizophrenia are more responsive and sensitive to treatment with an antipsychotic drug in terms of efficacy and side effects than patients with chronic schizophrenia (McEvoy *et al.*, 1991; Salimi *et al.*, 2009). Thus, the average dose of antipsychotics in first-episode patients is usually lower than that used with multi-episode patients (Robinson, 2010). Supporting this notion, we observed relatively lower doses of blonanserin in first-episode patients than in patients with chronic schizophrenia (see Results section).

In this study, EPS were observed in 55.0% of first-episode patients, and 25.0% of these patients required anticholinergic drugs. However, the mean dose of anticholinergics at endpoint was very low, and no severe adverse effects were observed during the study. Data on the safety of blonanserin in our sample will be described in detail in another report (Miyamoto *et al.*, unpublished results).

Limitations

There are several limitations in the current study. First, the sample size was small, making the results of this study vulnerable to type I and type II errors. Also, we did not include subjects with severe agitation, suicidal ideation, or substance dependence. Moreover, most subjects had the paranoid type of schizophrenia. It is thus unclear whether the present results are potentially generalizable to patients with first-episode schizophrenia in real-world settings. Our results will require replication in a larger cohort and over a longer term.

Second, as already mentioned, it was difficult to distinguish practice effects from placebo effects in the present study, although inclusion of a placebo-treated group was not viable for ethical reasons (Andersen *et al.*, 2011). Moreover, this study was underpowered to detect a practice effect on cognitive functioning because of the small sample size of the control group. The inclusion of a comparator antipsychotic in a double-blind fashion could have strengthened the conclusions to be drawn.

Despite these limitations, this study provides the first evidence for the ability of blonanserin to improve

cognitive function, psychopathology, and subjective QOL in first-episode schizophrenia. It has been reported that much of the deterioration (e.g., advancement of negative symptoms) associated with schizophrenia may occur during 2 to 3 years after the onset of illness (Birchwood *et al.*, 1998). Thus, treating patients with an antipsychotic with superior efficacy across a broad range of symptoms in the early stage is expected to improve long-term outcome (Miyamoto *et al.*, 2008; Robinson, 2010). In view of the results obtained in this study, blonanserin may be a promising candidate for a first-line antipsychotic for patients with first-episode schizophrenia.

CONCLUSION

Blonanserin may improve some types of cognitive function associated with the frontal lobe activity in patients with first-episode schizophrenia. Moreover, blonanserin may have beneficial effects on psychiatric symptoms and subjective QOL. Further studies with a larger sample size and longer duration of treatment are needed to confirm our observations.

CONFLICTS OF INTEREST

Dr Miyamoto has served as a consultant for Dainippon Sumitomo Pharmaceutical. He has received advisory board honoraria from Chugai Pharmaceutical. No other authors have any conflicts of interest with any commercial or other associations in connection with the submitted manuscript.

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ORIGINAL ARTICLE

Effectiveness of the Takeda Three Colors Combination Test as a screening test for dementia

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Abstract

Background: The aged population is increasing worldwide and it is expected that dementia, for which aging is a risk factor, will increase as well. A critical issue then becomes a community's capacity for the early detection of dementia among its senior citizens. In the present paper, we report on the development and potential use of a screening test for dementia that can be administered and assessed easily in a short period of time by non-specialist clinicians and represents no burden for those undergoing the screening.

Methods: Three hundred and sixty senior citizens, over 60 years of age, participated in the study. Of these, 126 had Alzheimer's disease (AD), 60 had vascular dementia (VaD), 41 had mild cognitive impairment (MCI), and 133 were healthy volunteers (control group). A screening test for dementia, which consisted of a colored cards configuration memory task (the Takeda Three Colors Combination Test; TTCC) was examined for sensitivity, specificity, reliability and criterion-related validity.

Results: Sufficient sensitivity and specificity were demonstrated for each clinical group (AD, VaD) and the control group. The sensitivity of the TTCC was 0.94, 0.82, and 0.71 for the AD, VaD, and MCI groups, respectively; specificity was 0.83. In addition, sufficient reliability and validity were established. Administration of the TTCCand assessment procedures required only 1 or 2 min.

Conclusion: Satisfactory sensitivity and specificity were indicated for both the AD and VaD groups, with sufficient reliability and validity also indicated. Thus, the TTCC is an effective dementia screening test.

Key words: *Alzheimer's disease, mild cognitive impairment, screening test for dementia, vascular dementia.*

INTRODUCTION

An increase in the elderly population has been seen not only in Japan, but also worldwide. According to a United Nations report,[1] by 2050 senior citizens will account for one-fifth of the world's population. As the elderly population increases, the need to manage dementia will also increase; this has become an international issue.

With an increase in the number of dementia cases, research efforts aimed at developing treatments for dementia have also increase, which has resulted in the development of acetylcholinesterase inhibitors, which slow the progress of Alzheimer's disease (AD) in its early stage.[2] Studies of an AD vaccine to decompose β-amyloid protien are also under way.[3] Some studies have reported on the efficacy of non-medical interventions, such as prevention programs for dementia, and cognitive rehabilitation, which is effective for mild cognitive impairment (MCI) and people with dementia in its early stages.[4,5] Delayed morbidity and the progression of dementia leads to a reduced need for care and a reduction in medical expenses. Thus, the early detection of dementia is becoming an increasingly important issue in mental gerontology.

However, because diagnosis of dementia in its early stages generally requires time, human resources, and

diagnostic imaging equipment, and is conducted within a special clinical setting, it is not unusual to find that the patient's condition has already progressed considerably by the time a diagnosis is made. It is estimated that 20–30% of elderly people in any one community experience dementia.[6,7] Aging is a major risk factor for dementia[8] and so early detection is important. In order to facilitate early detection, it is suggested that the screening test: (i) be easy to administer for non-specialists; (ii) imposes no strain on those undergoing the screening; (iii) be accomplished in a short period of time; and (iv) be easy to evaluate.

With these conditions in mind, Takeda *et al.* developed the Takeda Three Colors Combination Test (TTCC), an easy and time-saving screening test.[9] However, in their previous study the following problems remained: (i) vascular dementia (VaD) was not considered in their investigation, which is as typical a dementia as AD; (ii) the validity of the TTCC was not examined; and (iii) MCI was not investigated.

Thus, the aim of the present study was to determine whether the TTCC could be a useful screening test for dementia by comparing the results of the TTCC between the AD and control groups, as well as the VaD and control groups, and to calculate the screening's reliability and validity. In addition, we discuss the plausibility of the TTCC as a screening test for MCI by comparing results obtained using the test between the MCI and control groups.

METHODS

Subjects

There were 360 people included in the present study (both men and women) that were divided into four groups: AD, VaD, MCI and the control group (Table 1). The age of subjects in all groups was restricted over 60 years. The people in the AD and MCI groups were patients receiving treatment at the Department of Psychiatry, Tottori Seikyo Hospital, who were complaining of memory lapses. The people in the VaD group were patients with the same complaint who were either receiving treatment at the Department of Psychiatry or the Cranial Nerve Department in the hospital. The *Diagnostic Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[10] was used for the diagnosis of AD and VaD. People with mixed dementia were excluded from the present study. The people in the MCI group were patients who did not meet the criteria of any dementia, but who scored 0.5 on the Clinical Dementia Rating (CDR) scale[11] and over 21 on the Revised Hasegawa Dementia Scale (HDS-R),[12] based on the definition by Petersen *et al.*[13]

The control group consisted of patients who had undergone a brain examination at Tottori Seikyo Hospital, had no complaint of memory lapses, were not diagnosed as having dementia according to DSM-IV standards, showed no precipitant conditions of cognitive dysfunction on magnetic resonance imaging scans, and scored 25 or over on the HDS-R. The objectives and methods of the study were explained to the subjects (or their families) and consent was obtained prior to participation in the study.

Table 1 Subject characteristics

	AD group (n = 126)	VaD group (n = 60)	MCI group (n = 41)	Control group (n = 133)
Age (years)	72.6 (8.0)	71.5 (7.3)	70.6 (7.1)	68.1 (6.5)
No. men/women	42/84	35/25	14/27	46/87
HDS-R socre	14.7 (4.7)	15.7 (5.5)	23.5 (1.6)	28.4 (1.5)

Data shos the mean value, with the SD given in parentheses.
AD, Alzheimer's disease; VaD, vascular dementia; MCI, mild cognitive impairment; HDS-R, Revised Hasegawa Dementia Scale.

Procedures

About the test

The dementia screening test used in the present study was the TTCC developed by Takeda *et al.* in 2004.[9] The examiner was not told which of the four groups a patient belonged to. The test is described in more detail below.

Implements The following items were used: three wooden colored cards (red, blue, and yellow), each 5 cm^2 and 5 mm thick, and a card with a diagram of the three colored squares in a certain configuration. Hereafter, the card with the diagram is referred to as the model (Fig. 1).

Outline The model is presented to the subject for 5 s before it is hidden. Following a simple interference task (a mathematical calculation), the subject is asked to arrange the three wooden colored cards to match the configuration shown in the model.

Procedure The test procedure was as follows:

1. Show the subject the three wooden colored cards and confirm that he or she can distinguish the colors.

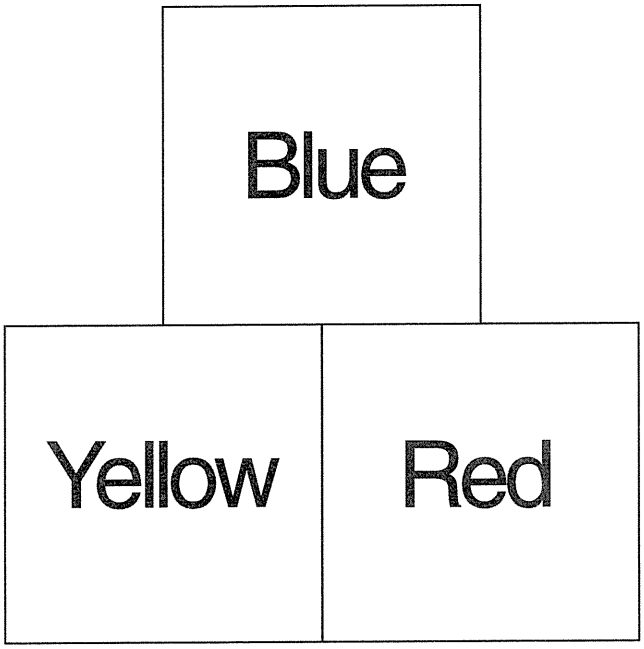

Figure 1 Arrangement of the three colored squares that should be remembered and reproduced later, after an interference task, using three wooden colored cards.

2. Explain what to do; for example, 'I'll show you a figure for 5 s, please remember it. I'll ask you to make the same figure from memory later using these three cards. Do you understand?' If the subject understands the instructions, hide the cards and proceed to the next step. If the subject does not understand, explain again.
3. Present the model for 5 s and then hide it quickly. Ask the subject, 'What is 100 minus 7?'
4. After the subject has answered the question, put the three colored cards in a pile and hand him or her the pile of cards. Ask the subject, 'Please make the same figure I showed you earlier'. Allow the subject 1 min to accomplish the task.

Conditions for stopping the test

The test is stopped if: (i) the subject is not able to complete the arrangement within 1 min; or (ii) the subject completes the arrangement within 1 min.

Assessment

If the subject succeeded in making exactly the same figure as shown in the model, he or she is assessed as being normal. If the arrangement of the colored cards differs from that shown in the model, dementia is suspected. Assessment does not include determing the correctness of the calculation, which is performed as an interference task.

Any of the following is regarded as an incorrect answer: (i) the cards overlap; (ii) the top square is placed off-center, such that the ratio of the lengths of the bottom side contacting the two lower squares exceeds 1.5; or (iii) the cards are arranged more than 5 mm apart.

Statistical analysis

The TTCC was administered to all groups. The difference between the control group and each of the other groups was examined using the Chi-squared test. The sensitivity of the TCC was calculated using data for each disease group who responded incorrectly in the first trial.

We conducted the TTCC again 1 month later for all groups, except the control group, to calculate the reliability of the test. The agreement between the first and second trials was calculated, as was the Phi coefficient.

Criterion-related validity was determined using HDS-R as an external criterion. With the TTCC, we allotted [1] to a correct response and [0] to an incorrect response as dummy variables and calculated Spearman's rank correlation coefficient between TTCC and HDS-R scores.

Concerning the age difference among groups, when a significant difference was detected in one-way analysis of variance, we once again allotted [1] to a correct response and [0] to an incorrect response as dummy variables to calculate Spearman's correlation coefficient between age and TTCC results. Concerning gender differences among groups, when a significant difference in gender ratio was detected among groups, we conducted a Chi-squared test to identify any relationship between gender and TTCC results.

RESULTS

Control group

In the control group, 110 people responded correctly and 23 responded incorrectly. Based on these results, the specificity of the TTCC is 0.83.

Comparison between the AD and control groups

In the AD group, seven patients responded correctly and 119 responded incorrectly (Table 2). Thus, the sensitivity of the TTCC was 0.94 for the AD group. In the Chi-squared test (AD group [2] × Control group [2]),

Table 2 The number of correct and incorrect responses to the Takeda Three Colors Combination test in each group

	Correct response	Incorrect response	Total
Control group (*n*)	110	23	133
AD group* (*n*)	7	119	126
VaD group** (*n*)	11	49	60
MCI group*** (*n*)	12	29	41

*Alzheimer's disease (AD) versus control: $\chi^2 = 155.5$, d.f. = 1, $P < 0.001$; **vascular dementia (VaD) versus control: $\chi^2 = 73.3$, d.f. = 1, $P < 0.001$; ***mild cognitive impairment (MCI) versus control: $\chi^2 = 42.7$, d.f. = 1, $P < 0.001$.

the difference in the performance of the TTCC between groups was significant ($\chi^2 = 155.5$; $P < 0.001$). The analysis revealed a significantly increased number of incorrect responses in the AD group and correct responses in the control group.

Including the results of the second trial in the AD group, five patients responded correctly in both trials, two responded correctly in the first trial but incorrectly in the second trial, 116 responded incorrectly in both trials, and three responded incorrectly in the first trial but correctly in the second trial.

Comparison between the VaD and control groups

In the VaD group, 11 patients responded correctly to the TTCC and 49 responded incorrectly (Table 2). Thus, the sensitivity of the TTCC for the VaD group was 0.82. In the Chi-squared test (VaD group [2] × Control group [2]), the difference between groups was significant ($\chi^2 = 73.3$; $P < 0.001$). The analysis revealed a significantly increased number of incorrect responses in the VaD group and correct responses in the control group.

Including the results of the second trial for the VaD group, seven patients responded correctly in both trials, four responded correctly in the first trial but incorrectly in the second trial, 49 responded incorrectly in both the first and second trails, and none responded incorrectly in the first trial but correctly in the second trial.

Comparison between the MCI and control groups

In the MCI group, 12 patients responded correctly to the TTCC and 29 responded incorrectly (Table 2). Thus, the sensitivity of the TTCC for the MCI group was 0.71. In the Chi-squared test (MCI group [2] × Control group [2]), the difference between groups was significant ($\chi^2 = 42.7$; $P < 0.001$). Secondary analysis showed a significantly increased number of incorrect responses in the MCI group and correct responses in the control group.

Including the results of the second trial for the MCI group, 11 patients responded correctly in both trials, one patient responded correctly in the first trial but incorrectly in the second trial, 24 responded incorrectly in both trials, and five responded incorrectly in the first trial but correctly in the second trial.

Reliability of the TTCC

Including the results of the second trials in the AD, VaD, and MCI groups, a total of 23 patients responded correctly in both trials, seven responded correctly in the first trial but incorrectly in the second trial, 189 responded incorrectly in both trials, and eight responded incorrectly in the first trial but correctly in the second trial. The Phi coefficient was 0.72 and the consistency percentage between the first and second trials was 93.4%.

Validity of the TTCC

Spearman's rank correlation analysis, using HDS-R as an external standard, revealed a significant correlation between the HDS-R score and results of the TTCC (Rho = 0.66; $P < 0.01$).

Age and gender differences between groups

One-way analysis of variance using 'age' as a dependent variable and 'group' as an independent variable yielded a significant effect of 'group' ($F_{(3)} = 8.98$; $P < 0.001$). In Tukey's multiple comparison analyses, a significant difference was obtained between the control and AD groups, as well as between the control and VaD groups. However, Spearman's Rho between age and the TTCC outcomes was not significant (Rho = –0.10).

The difference in gender ratio among groups was significant ($\chi^2 = 12.6$; $P < 0.01$) using the Chi-squared test (group [4] × gender [2]). Secondary analysis revealed that the VaD group was comprised of significantly more men and fewer women compared with the control group. However, the Chi-squared test (gender [2] × the TTCC outcomes [2]) for all subjects revealed no significant relationship between gender and TTCC outcomes ($\chi^2 = 0.15$).

Time requirements for the TTCC

The TTCC (including instruction and assessment) was accomplished within 1 min for 78% of subjects and

within 2 min for 22% of subjects. No refusal or resistance to this test was observed by any of the subjects.

DISCUSSION

Effectiveness of TTCC in screening for dementia

We have suggested the importance of screening for dementia in the community. However, it is not plausible to accomplish dementia screening in the community using only a limited number of specialists. If we are to take effective measures against dementia, naturally we need to develop a screening test that can be administered and assessed simply and quickly by non-specialists.

The leading cause of dementia is AD, followed by VaD. These two types of dementia together account for 70–80% of all dementia cases.[14,15] Thus, any screening test developed should enable detection of both AD and VaD. The TTCC screening test meets these criteria, as demonstrated in the comparisons of the AD, VaD, and control groups.

First, a significant difference was found between the AD and control groups. The sensitivity of the test was 0.94 and specificity was 0.83. Second, were able to differentiate the VaD group, which was investigated for first time in the present study, from the control group with a sensitivity of 0.82.

The relatively high sensitivity of the TTCC test for AD shown in the screening is explained by the fidelity of the TTCC in detecting impairment in recent memory and space perception, both of which are seen in the early stages of AD.[16] Recent memory, among all memory classifications, is the one damaged at the earliest stage of AD.[17] A recent memory task requires subjects to recall items after a short interval, during which an interfering task has been inserted.[18] With the TTCC, although there is no appreciable time lapse following memorization, an interfering task is imposed before the subject is required to retrieve the model, implicating recent memory rather than immediate icon memory.

The TTCC is also relevant to visuospatial cognition, because the subject is required to reconstruct the spatial arrangement of the cards from visuospatial memory of the model figure. Impairment in visuospatial cognition is prominently seen at an early stage of AD.[19]

The sensitivity of the test in diagnosing VaD was somewhat less than that for AD. We consider this is because the main symptoms of VaD are not necessarily impairments in recent memory or visuospatial cognition. Cognitive impairments of VaD are more varied than in AD depending on the area of the brain that is damaged.[20]

Despite the difference in sensitivity of the TTCC for AD and VaD, the detection rate compares favorably with other screening tests for AD and VaD.[21–23] Therefore, it may be assumed that the TTCC is as effective a screening test for both AD and VaD.

As for the time required to administer the TTCC, in all cases the task was completed within 2 min, with most people able to complete the task in less than 1 min. Considering that subjects tend to get tired easily and experience a decline in attention and concentration, screening tests should be conducted as promptly as possible. Thus, the short time required to administer the TTCC makes it an appropriate screening test for seniors. None of the subjects refused to take the TTCC and none showed any resistance during the task. The task of remembering a figure and reproducing it was accepted as enjoyable, motivating subjects to participate in the screening. In fact, with other widely used screening tests, such as the Mini-Mental State Examination, some subjects may get embarrassed or sometimes refrain from taking the task because of the offensive content of some of the test items.[22] In this light, the TTCC is taken not as unpleasant as some other tests.

The effectiveness of the TTCC as a screening test for MCI was also examined in the present study. Comparing MCI and control groups indicated a significant difference in the number of correct responses, but the sensitivity of the TTCC for MCI was 0.71, which is not high. We cannot determine whether the TTCC is an effective screening test for MCI.

Validity and reliability of the TTCC

The TTCC was administered to subjects again after 1 month, except for the control group, to determine its reliability. Considerable correlation in the Phi coefficient was indicated between the first and second trials. The consistency score was also very high. These results are almost equal to those of our previous study.[9] As for inter-rater reliability, taking into account that the TTCC is quite simple to administer and requires no special training, the effect of the examiner on the results was thought to be negligible. Given the results noted above, we may say that the TTCC is a highly reliable screening test for dementia.

Criterion-related validity, measured with the HDS-R as an external standard, indicated a rather high correlation between the TTCC results and HDS-R scores. Because the HDS-R is widely used in Japan, we think that the high correlation between the TTCC results and HDS-R scores suggests the criterion-related validity of the TTCC as a screening test for dementia.

Significant differences were obtained among groups in age and gender ratio; however, no significant relationship was shown between these factors and the TTCC results. Therefore, we did not take into account these factors in statistical tests.

Effectiveness of the TTCC as a medical checkup tool

The importance of detecting dementia in aged individuals is growing as the aged population increases. It is desirable that a screening test that can be administered by non-specialists be developed.

Takayama[23] suggests that if screening is to be conducted quickly in locations other than hospitals by non-specialist clinicians in the field of neuropsychology, then the first structural condition to be met is that the test be easy to take, as well as motivating, for both the aged who are otherwise healthy and those who are cognitively impaired. The equipment should be low cost and the procedure simple.

The results of the present study have shown that the TTCC is satisfactory in terms of sensitivity and specificity and that it is an effective screening test for dementia, with adequate reliability and criterion-related validity. It is administered quickly and was accepted favorably by all subjects. It requires no special training or techniques to administer. Therefore, we can say that the TTCC is an easy-to-use screening test, especially effective for use in the community.

The content of the TTCC test is quite simple and so the user's education or cultural background, or even language, is likely to have little effect on the outcome. Given also that it requires little in terms of equipment expenditure, the TTCC appears to be well suited for worldwide use as a screening test for dementia.

Limitations and problems to be overcome in the present research

The present study examined the usability of a screening test developed for dementia. Because the principal aim of screening tests is early detection, it would have been preferable to include more subjects at early stages with mild dementia. However, most subjects in the present study were patients with relatively severe advanced AD and VaD. An MCI patient group was included in the present study and the sensitivity of the TTCC for MCI was approximately 70%. However, it has been reported that approximately 50% of subjects diagnosed with MCI show improvement in subsequent screening tests.[24,25] Therefore, the validity of the TTCC for detecting those MCI patients who develop dementia in the future is not yet clear. It would be of considerable interest to follow those subjects with MCI who responded incorrectly in the TTCC in the present study to see whether they actually convert to dementia at some time in the future.

The subjects in the present study were all patients of a single medical institute, making it difficult to generalize the results across samples. Further testing with patients from a number of medical institutions from different areas will enable the results to be standardized, enhancing the usability of the TTCC.

In order to strengthen the benefit of the TTCC as a screening test used worldwide, it is also worth investigating its relevance to biological indices, such as functional neuroimaging findings, in future studies.

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Regular Article

Does daily Naikan therapy maintain the efficacy of intensive Naikan therapy against depression?

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Aim: Naikan Therapy, which has been applied to treating patients with various mental difficulties, can be classified into two major categories: intensive Naikan therapy, which lasts for seven days in a Naikan center or a clinical institute secluded from the outside world for the purpose of deep introspection, and daily Naikan therapy, which can be integrated into regular daily activities. The aim of this research is to evaluate daily Naikan therapy as a maintenance treatment for depression.

Methods: Forty-seven patients, who were diagnosed as having major depressive disorder using DSM-IV criteria and who practiced intensive Naikan therapy participated in the present study. Two groups of patients were compared: 24 patients who conducted daily Naikan therapy and 23 patients who did not, after practicing intensive Naikan therapy. To evaluate efficacy, the Beck Depression Inventory was used as a primary outcome measure for the assessment of depression. The State–Trait Anxiety Inventory and the Cornell Medical Index were also used as secondary outcome measures to evaluate anxiety and psychosomatic conditions before, immediately after and three months after intensive Naikan therapy.

Results: Significant between-group differences were obtained in the time course change of depression, anxiety and psychosomatic scores within three months following the completion of intensive Naikan therapy.

Conclusion: The current study indicates that conducting daily Naikan therapy is effective for maintaining the psychological and psychosomatic state at 3 months following the intensive Naikan therapy, while a lack of therapy may allow the patients to exacerbate their conditions to the level they held before practicing intensive Naikan therapy.

Key words: anxiety, daily Naikan therapy, depression, intensive Naikan therapy, psychosomatic condition.

MAJOR DEPRESSION MAY require long-term treatment because it is a debilitating and recurrent disorder.[1] Efficacious alternatives to medication, including psychological intervention, are necessary, especially for patients who may not tolerate or respond to medication. Approximately 40% of patients with depression discontinue their medication within the initial 30 days, and the dropout rate even reaches 72% within 90 days after starting medication.[2–4] A meta-analysis study comparing the efficacy between pharmacotherapy and psychotherapy in patients with depression reported that both were about equally effective, whereas the dropout rates seemed to be smaller in psychotherapy compared with pharmacotherapy.[5] Moreover, a systematic review comparing both the efficacy and adherence to antidepressant medication use between antidepressant treatment in combination with a psychological intervention and antidepressant treatment

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alone indicated that the former was associated with a higher improvement rate that the latter.[6] In longer therapies, the combination with psychotherapy significantly reduced the dropout rates. However, most studies cited in the above reviews are those from Western countries, and the psychological interventions adopted are cognitive–behavioral therapy, interpersonal psychotherapy, problem-solving therapy and others.

Naikan was established by Ishin Yoshimoto (1916–1988), who was a Jodo Shin Buddhist minister. Naikan literally means 'looking within'. Naikan was originally rooted in a spiritual practice called *Mishirabe*, which was practiced among Jodo Shin Buddhist followers in a rural district in Nara, Japan, where Yoshimoto was born. In the practice of *Mishirabe*, in addition to introspection, the practitioners fasted completely even without liquids, and went without sleep for long periods to reflect on their thoughts and behaviors. What Yoshimoto discovered through this practice was the degree to which his life had been sustained by others, by all living creatures and ultimately by nature instead of only through self-centeredness and, by extension, ignorance. Based on his experience, Yoshimoto realized the possible use of this therapy for all people, not only Buddhist practitioners. So, he established a relatively easier method by eliminating the strict physical restrictions and formed three themes for 'healthy' practitioners to be discussed later. Nowadays, the main goal of Naikan is not to achieve religious enlightenment, but to experience self-understanding and self-improvement, goals that can be applied to any person regardless of religion, ethnic group or social background. Naikan therapy (NT) has been adapted to prisons, detention homes, schools and business training. In the field of psychiatry, it has been reported that Naikan as psychotherapy is an efficient means of treating patients with various mental difficulties.[7]

In intensive Naikan therapy (INT), the patient sits in the corner of a room, walled off by a folding screen to cut off visual stimulation from the outside so that it is easier for them to observe their own thinking. Sitting in a quiet place and staying in a relaxed position, the patient begins to seriously look into his/her thoughts, continuing his/her introspection daily from 06.00 hours to 21.00 hours. The patients examine how they have lived according to three themes: (i) What have I received from a particular person? (ii) What have I returned to that person? and (iii) What troubles and difficulties have I caused that person? To begin with, the patients are asked to examine the relationship with their mothers or their main caretakers through every period of their life, starting from childhood and gradually moving to the present. Then, they are asked to examine themselves regarding other people who are close to them, such as their fathers, spouses, friends, colleagues, and so forth.

In their articles, both Tashiro,[8] who studied the efficacy of INT for prolonged depression, and Nukina,[9] who presented the efficacy of INT for general anxiety disorders and panic disorders, have referred to the importance of daily Naikan therapy (DNT) as an important factor for preventing the recurrence of various mental disorders, although detailed data have not yet been provided. Yoshimoto, the founder of Naikan, emphasized to his clients that doing DNT for at least one hour a day after completing INT would be highly beneficial.[10] He insisted that INT is the preparation for DNT, which should be integrated into daily life. His view was that, although the patients successfully completed INT, their neglect of DNT may cause a quick recurrence of their original perspectives and habits. Yoshimoto's encouragement to do DNT could be explained by his understanding of Dr Ikemi's argument that the neocortex of humans completes its development by the age of 15–16, so the character of each person has generally been formed around that time and is thus very difficult to change. The paleocortex is more fragile and sensitive than the neocortex to various stressful conditions humans are exposed to. These experiences, especially emotional ones experienced by infants through interaction with parents and others, greatly influence the formation of their personalities. The pathetic characteristics of some patients cannot form by experiences and memories from their childhood unless they are recognized and, thus become deeply rooted in their consciousness.[11] Therefore, even though patients experience dramatic transformation by practicing INT, by ignoring DNT, they would be drawn to their previous habits and perspectives and may have additional episodes.

The method of DNT for patients who do it for one hour a day is as follows. Patients examine their past as they did in INT. They divide their lives into chronological segments and reflect on themselves in relation to persons important in their lives for half an hour each day as they did in INT. For example, at the end of the day one patient may examine his/her

relationship with his/her mother from three to six years for half an hour. Then, the patient may use the remainder of the hour examining his/her day according to the three Naikan themes as follows: (i) What did I receive from others today? (ii) What did I give to others? and (iii) What troubles and difficulties did I cause others today? He/she may then go on to examine a later period of life, for example, four to seven years, on the following day for half an hour, then use the remaining half hour to ask himself/herself the three Naikan themes for that day.

The purpose of this research is to evaluate the efficacy of DNT as a maintenance treatment for depression by comparing patients: (i) who experienced INT and continued DNT, with (ii) those patients who did not conduct DNT after practicing INT. To evaluate efficacy, the Beck Depression Inventory (BDI) was used as a primary outcome measure and the State–Trait Anxiety Inventory (STAI) and the Cornell Medical Index (CMI) were used as secondary outcome measures before, immediately after and three months after INT.

METHODS

Subjects

The subjects were 47 inpatients who were diagnosed as having major depressive disorder through interviews and close examination according to DSM-IV criteria[12] by an experienced psychiatrist. All subjects underwent INT at the Midorigaoka Mental Health Clinic between July 2006 and February 2008. The patients with strong suicidal tendencies, paranoia and severe depression requiring psychophysical restraint were excluded. All of the subjects gave written informed consent before participating.

Study design

All subjects had completed INT shortly before they were discharged from the Midorigaoka Mental Health Clinic. Immediately after the completion of INT and at discharge, all patients were advised to practice DNT. However, 24 patients consented to practice daily Naikan (DNT group) while 23 did not (non-DNT group) owing to participant-determined attendance. Fifteen out of 24 patients in the DNT group were admitted to hospital with the aim of undergoing INT for 7 days, which was designated as 8 days for the length of hospitalization. As for the nine patients, they were recommended to practice INT during their stay in the hospital and the average length of hospitalization of these nine patients was 58.3 days. Thirteen out of 23 patients in the non-DNT group were admitted to hospital with the aim of undergoing INT. The rest of the patients were recommended to practice INT during their stay in hospital and the average length of hospitalization of these subjects was 50.2 days. There was no significant between-group difference either in the rate of the patients admitted to hospital with the aim of undergoing INT or the length of hospitalization. Other clinical and demographic backgrounds at baseline for both groups immediately after INT completion are shown in Table 1. All subjects were assessed immediately before and after INT, and after the three months' trial starting shortly after INT completion for depression, anxiety and psychosomatic symptoms severity. The DNT group complied fairly well with the one-hour/day session of DNT within the three months' period and the average rate of practicing the therapy was 3.5 days/week. Twenty-two out of 24 patients in the DNT group were under medication during the trial, which was similar to 22 out of 23 in the non-DNT group.

Assessments

1 Psychological scales

The BDI,[13] the STAI,[14] and the CMI[15] tests were used for evaluation. The CMI was adopted to observe whether physical functions of patients would be normalized as patients became mentally stable from the perspective of psychosomatic medicine. In cases where NT helped to make patients mentally stable, stress would be alleviated and physical functions would also be normal.[16] Therefore, various subjective somatic symptoms (such as hearing, visual, cardiac, respiratory, gastro, dermatological, neural, urological and fatigue symptoms) and subjective psychological symptoms of depression (such as anxiety, tension, hypersensitivity, indignation and inadaptability) may differ between those patients practicing DNT and those not practicing DNT.

2 Quality of Naikan: Evaluation after the completion of INT in terms of psychological transformation

It is desirable in NT to recall events in the past by taking another person's perspective along with seri-

Table 1. Clinical and demographic background of the subjects

	DNT	non-DNT	*P*-value
Number of subjects	24	23	
Male subjects	9	16	$P < 0.05^{\dagger}$
Mean age (SD)	38.5 (11.0)	32.7 (12.5)	n.s.[‡]
Subjects with single episode	16	17	n.s.[†]
Mean years of illness duration (SD)	1.7 (1.7)	1.7 (1.5)	n.s.[‡]
Frequency of practicing DNT			
Everyday	3	0	
5–6 times per week	2	0	
3–4 times per week	13	0	
1–2 times per week	6	0	
Mean BDI scores (SD) before INT	25.1 (7.8)	25.5 (10.4)	n.s.[‡]
Mean STAI trait scores (SD) before INT	51.0 (12.5)	58.5 (13.7)	n.s.[‡]
Mean STAI state scores (SD) before INT	49.5 (12.2)	52.7 (17.3)	n.s.[‡]
Mean CMI-soma scores (SD) before INT	27.0 (18.5)	40.9 (21.7)	$P < 0.05^{\ddagger}$
Mean CMI-psyche scores (SD) before INT	16.7 (10.8)	22.3 (13.5)	n.s.[‡]

[†]Chi-square test.
[‡]Wilcoxon's rank sum test.
BDI, Beck Depression Inventory; CMI-psyche, Cornell Medical Index, psychological; CMI-soma, Cornell Medical Index, somatic; DNT, daily Naikan therapy; INT, intensive Naikan therapy; n.s., not significant; SD, standard deviation; STAI, State–Trait Anxiety Inventory.

ously considering the three already mentioned main themes. As a result, patients may realize that they have received so much love and care from others (feelings of being loved), and will recognize a self-centeredness that they never realized before. When they seriously feel guilt and remorse, they may decide that they would like to discard their ego-centeredness. As discussed above, in terms of psychological transformation, the factors for evaluation are: (i) seeing things from another person's perspective; (ii) the feeling of being loved; (iii) awareness of ego-centeredness; and (iv) the decision to discard ego-centeredness. These four categories are evaluated as shown in Table 2.[17]

In addition to the above four categories, questions as to whether the patients had a sense of accomplishment and self-acceptance after INT were also added for evaluation.

Table 2. Criteria for evaluation of the four categories of psychological transformation

Psychological transformation		Score
Seeing things from another person's perspective	seeing things only from the patient's perspective	0
	seeing things objectively without personal emotions	1
	seeing things from the other person's point of view	2
Feelings of being loved	no feelings of being loved	0
	feelings of being loved	1
	feelings of being loved unconditionally despite the problems to the person	2
Awareness of ego-centeredness	no ability to be aware of ego-centeredness	0
	only aware of ego-centeredness	1
	awareness of ego-centeredness and remorseful and/or guilty feelings	2
Decision to discard ego-centeredness	no ability to be aware of ego-centeredness	0
	only aware of ego-centeredness	1
	a decision to discard ego-centeredness	2

Data analysis

First between-group differences were tested using χ^2-tests for dichotomous variables and Wilcoxon rank sum tests for continuous variables in terms of clinical and demographic backgrounds of the DNT and non-DNT groups. Moreover, assessments regarding psychological transformation after INT were compared between the two groups. In addition, to assure the efficacy of INT for depression, we calculated the remission rate according to the definition of the BDI $\leqq 8$.[18] Next, a repeated ANCOVA measure was performed using the BDI, STAI-trait (T), STAI-state (S), CMI-somatic (soma) and CMI-psychological (psyche) scores as dependent variables; group and sex as interindividual factors; time of assessment (before INT, immediately after INT, 3 months after INT) as an intraindividual factor; and the clinical, demographic and psychological transformation data as covariates if they showed significant between-group differences either before or immediately after INT. For the variables that showed significant interaction between group and time, the difference scores between the first and second assessments (difference-INT) and those between the second and third assessments (difference-DNT) were submitted for secondary ANCOVA.

As depression, anxiety and psychosomatic symptoms are assumed to hold a correlative relationship with each other, the effect of DNT on depression may well be obtained indirectly via its efficacy on anxiety and/or psychosomatic symptoms. With the aim of investigating whether the effect of DNT on depression is independent from its efficacy on anxiety and/or psychosomatic symptoms, we calculated Spearman's rank correlation coefficient between each pair of the difference-DNT variables of BDI, STAI-T, STAI-S, CMI-soma and CMI-psyche scores. Next, in case significant correlations were observed between at least some pairs, we reanalyzed whether significant between-group differences could be obtained in difference-DNT BDI scores, including those variables as covariates that showed a significant relationship with difference-DNT BDI scores in additional ANCOVA.

RESULTS

First, the number of patients that attained the remission criteria immediately after INT was 18 (38.3 %) in total. A significant between-group difference was scored for the number of remitted patients, that is, there were 13 out of 24 patients (54.1%) in the DNT group whereas there were five out of 23 (21.7%) in the non-DNT group ($P < 0.05$, χ^2-test). Next, as there were significant between-group differences in sex, CMI-soma scores assessed before INT, and the scores for 'feelings of being loved' and 'the decision to discard ego-centeredness' after INT (see Table 3), we adopted the latter three variables as covariates and added sex as an interindividual variable in the following repeated measures ANCOVA.

BDI

There was a significant interaction between group and time ($F [2, 80] = 23.31$, $P < 0.0001$) along with a significant main effect of time. The secondary analyses revealed significant between-group differences in both difference-INT ($F [1, 40] = 4.79$, $P < 0.05$) and difference-DNT scores ($F [1, 40] = 34.72$, $P < 0.0001$) (Fig. 1).

Table 3. Comparison of the psychological transformation after INT between the DNT and non-DNT subjects

	DNT	non-DNT	*P*-value
Psychological transformation			
Seeing things from another person's perspective; mean (SD)	2.7 (0.5)	2.4 (0.8)	n.s.‡
Feelings of being loved; mean (SD)	2.7 (0.5)	2.3 (0.8)	$P < 0.05$‡
Awareness of ego-centeredness; mean (SD)	2.7 (0.5)	2.5 (0.6)	n.s.‡
Decision to discard ego-centeredness; mean (SD)	2.5 (0.7)	2.0 (0.7)	$P < 0.05$‡
Number of subjects who gained a sense of accomplishment	24	21	n.s.†
Number of subjects who gained a sense of self-acceptance	22	18	n.s.†

†Chi-square test.
‡Wilcoxon's rank sum test.
DNT, daily Naikan therapy; INT, intensive Naikan therapy; n.s., not significant; SD, standard deviation.

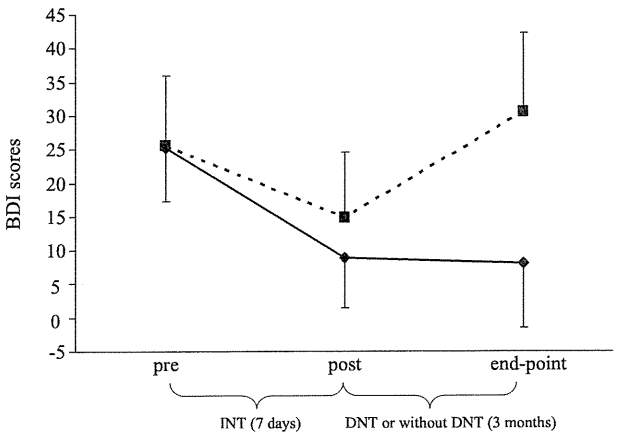

Figure 1. Comparison of Beck Depression Inventory (BDI) scores between (-◆-) the daily Naikan therapy (DNT) and (-■-) non-DNT subjects at pre, post and 3 months following intensive Naikan therapy (INT). INT was conducted for 7 days between 'pre' and 'post', and DNT for 3 months between 'post' and 'end-point' for DNT subjects but not for non-DNT subjects. The vertical bars indicate standard deviations. Note the improvement in DNT subjects exceeded that in non-DNT subjects in either difference-INT (pre-post) or difference-DNT (post-end-point) scores.

STAI

For either STAI-T or STAI-S scores, there was a significant interaction between group and time (Table 4). The secondary analyses revealed a significant between-group difference in difference-DNT for either STAI-T ($F [1, 40] = 17.71$, $P < 0.0001$) or STAI-S scores ($F [1, 40] = 19.49$, $P < 0.0001$), but not in difference-INT scores.

CMI

For either CMI-soma scores or CMI-psyche scores, there was a significant interaction between group and time (Table 4). The secondary analyses revealed a significant between-group difference in difference-DNT for either CMI-soma ($F [1, 40] = 22.81$, $P < 0.0001$) or CMI-psyche scores ($F [1, 40] = 14.05$, $P < 0.001$), but not in difference-INT scores.

Relationship between difference-DNT BDI, STAI and CMI scores

Spearman's rank correlation coefficient between each pair of the difference-DNT variables of BDI, STAI-T, STAI-S, CMI-soma and CMI-psyche scores revealed that all the pairs showed significant correlations (rho = 0.45–0.70). Additional ANCOVA using difference-DNT BDI scores as dependent variables, including those variables as covariates that showed a significant relationship with difference-DNT BDI scores revealed the non-significant effect of the group ($F [1, 36] = 3.27$, $P < 0.1$).

DISCUSSION

Despite the shortcomings in the present study design as noted below, whereas BDI showed significant between-group differences in the improvement during both DNT and INT, significant between-group

Table 4. Comparison of secondary outcomes between the DNT and non-DNT subjects at pre, post and 3 months following intensive Naikan therapy

Measures	Group	*time*	Pre	Post	End-point	Analysis
STAI-T	DNT		51.0 (12.5)	43.5 (13.5)	37.1 (10.3)	F (2, 80) = 11.71
	non-DNT		58.5 (13.7)	51.7 (15.1)	58.9 (12.6)	$P < 0.0001$
STAI-S	DNT		49.5 (12.2)	32.0 (9.9)	35.2 (11.7)	F (2, 80) = 9.24
	non-DNT		52.7 (17.3)	38.1 (14.8)	56.2 (14.6)	$P < 0.0005$
CMI-soma	DNT		27.0 (18.5)	20.9 (18.8)	19.4 (16.0)	F (2, 80) = 12.92
	non-DNT		40.9 (21.7)	30.8 (18.6)	46.6 (24.0)	$P < 0.0001$
CMI-psyche	DNT		16.7 (10.8)	9.8 (10.9)	8.1 (10.1)	F (2, 80) = 7.24
	non-DNT		22.3 (13.5)	16.9 (10.5)	24.3 (13.7)	$P < 0.005$

Analysis: interaction between time and group in repeated measures ANCOVA.
CMI-psyche, Cornell Medical Index, psychological; CMI-soma, Cornell Medical Index, somatic; DNT, daily Naikan therapy; STAI-S, State–Trait Anxiety Inventory-State; STAI-T, State–Trait Anxiety Inventory-Trait.

differences were noted specifically in the DNT phase in terms of STAI and CMI. Therefore, the present findings suggest the efficacy of DNT in preventing the exacerbation of depression by maintaining at least the anxiety and psychosomatic state within three months following the INT. As for depression, as a significant between-group difference was already evident in the INT phase, the possibility cannot be ruled out that the effect of INT was stronger and more extensive in the DNT group than in the non-DNT group. Moreover, an additional analysis testing the effect of DNT on depression using the efficacy of DNT on anxiety and psychosomatic symptoms as covariates suggested the possibility that the effect was indirectly obtained via its efficacy on anxiety and/or psychosomatic state.

It is necessary here to mention the limitations of the present study. Although the definition of 'maintenance treatment' has not been firmly established,[19] the common consensus understood by professionals refers to a longer period of treatment after the acute symptoms of a disorder have been resolved and the patient has been asymptomatic for at least a six-month period.[20] Therefore, a further research using a longer treatment period should be encouraged to confirm the efficacy of DNT as a 'maintenance' therapy.

In this study, as the patients themselves decided whether they would practice DNT or not, the subjects were not assigned randomly. The DNT and the non-DNT groups were significantly different in several points of their demographic and clinical background as shown in more women and lower mean CMI-soma scores in the DNT group before INT. Moreover, as compared to the non-DNT group the patients in the DNT group were those that showed a better response to INT, as shown in the improvement of BDI scores and the remission rate defined by BDI, which may well lead to a strong bias to practice DNT. Therefore, it is by no means clear whether DNT is effective or not until a randomized assignment design is adopted. There is a possibility that NT may not be adaptable to some patients' inclination and in such cases, DNT would not work effectively on them as a maintenance therapy either. In addition, we used only subjective questionnaires for the assessment, which might have caused a bias towards the good efficacy for DNT, especially because the subjects in the DNT group decided themselves to practice DNT and were consequently highly motivated. Further studies using a randomized assignment design and objective measurements for assessment are warranted in order to evaluate the accurate efficacy of DNT avoiding any selection biases.

It has been argued that the continuous practice of DNT is not easy. One study showed that at a Naikan center for mentally healthy people, two years after INT, only about half of the practitioners continued DNT.[21] Therefore, for patients to practice DNT, they may require strong motivation and discipline for successful treatment. Some device or scheme to conduct DNT more easily should be considered.

NT starts with renewing understanding of others by recollecting memories with other persons' perspectives. Awareness of ego-centeredness and a sense of being loved allows the patient to experience the cognitive transformation from a victim into a person who has been loved and sustained by others. When a person has strong ego-centeredness, he/she becomes inconsiderate, unsatisfied and even criticizes others. This would lead the person into a cycle of bad interpersonal relations and isolate himself/herself from society and cause depression as the result.[22] NT juxtaposes the human selfishness and failures that result from our weakness with the caring concern of others and suggests that the natural response to recognition of this discrepancy will be gratitude and a desire to serve others. Thus, the realization of one's own unworthiness, imperfection and sinfulness leads not to the hell of depression but to a positive thankfulness and life purpose.[23] Therefore, NT is adequate and recommended to both mentally unhealthy and healthy people, especially to those who have a tendency to blame others, to feel unworthiness and to suffer from poor interpersonal relationships. Also, family members of patients are strongly recommended to practice INT because patients' psychological and social environment should be considered; relationships with parent(s) and spouses may be factors for depressive symptoms in patients.[24]

On the other hand, in the present study, three patients in the non-DNT group mentioned they were not confident to practice DNT without a Naikan *mensetsusha* (therapist) as NT tends to focus on negative aspects of their memories and make them feel depressed. For severe cases with depression, especially in case the client tends to blame himself/herself strongly, introduction of INT is inadequate at least until depressive symptoms become relatively stable and signs of strong motivation appear, considering a case report of a patient who attempted suicide during an INT session.[25]

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