

Dementia: Advances and Treatment

Chapter 3

Neurological Background in a Comprehensive Approach of Psychosocial Intervention Combined with Drug Treatment for QOL in Alzheimer Disease: the Osaki-Tajiri Project

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1. Introduction: QOL and the Bio-Psycho-Socio-Spiritual Model of Health

The World Health Organization (WHO) defines health in terms of “Quality of Life (QOL) as an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” [1]. The basic concept of QOL includes categories such as physical function and mental health. However, actual health-related QOL is a complex problem since most elderly people have several chronic diseases and decreased physical functions with aging.

The WHO also defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” [2]. This is the basis of the Bio-Psycho-Socio-Spiritual (BPSS) model. A comprehensive approach for patients with dementia based on this model is shown in **Figure 1**. A pharmacological approach (drug treatment) affects “Bio” directly, while non-pharmacological approaches (psychosocial interventions) influence the “Bio”, “Psycho”, “Socio”, “Spiritual” parts of the model.

A striking kanji character, which is now used only in Taiwan (but was used in Japan before World War II) that means “medicine” is shown in **Figure 2**. The left upper part literally shows containers of arrows, indicating biological effects. The right upper part reflects psychosocial issues, suggesting a “doctor-patient relationship.” The bottom part shows spiritual issues. The Japanese Kun-reading of this kanji character is “to care.” This is an old traditional sense of health that is not far from the WHO concept.

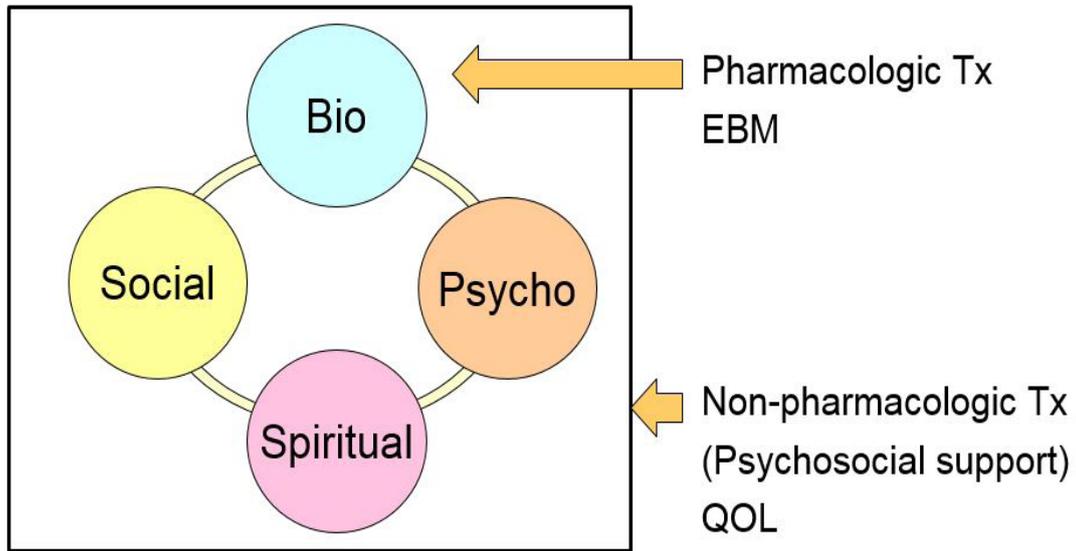


Figure 1: Concept for health (WHO):BPSS model: Comprehensive intervention for dementia

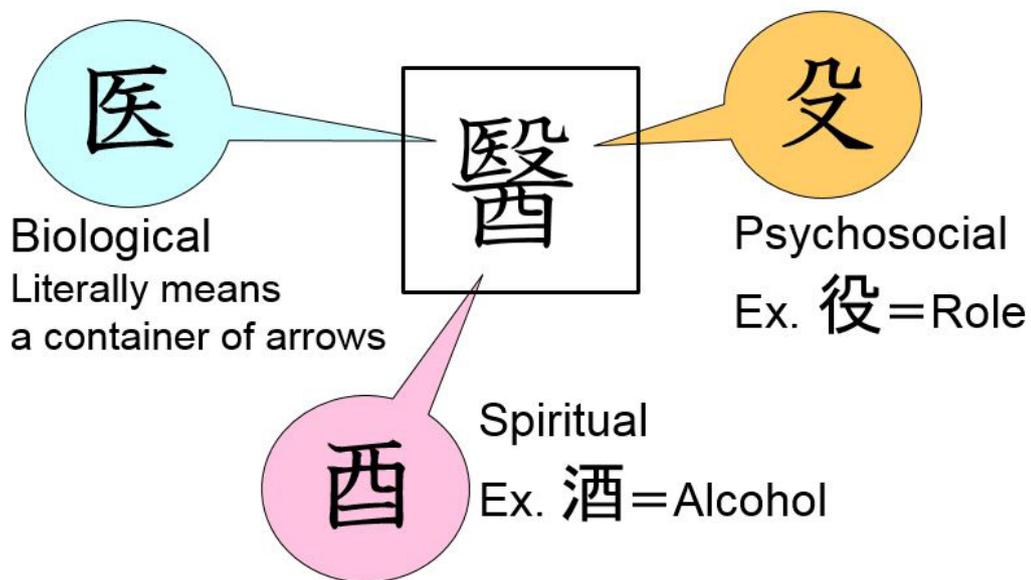


Figure 2: Medicine= Bio-PsychosocioSpiritual as illustrated by Kanji

2. Case report

We here describe a previously reported case [3], since this is a good case for considering QOL as an outcome of a comprehensive approach.

2.1. A patient with severe Alzheimer disease

The patient was a right-handed, 79-year-old woman with 10 years of school education. She had no remarkable medical history and no family history of dementia. She had worked as a nurse and was also an experienced and licensed professor of Japanese flower arranging (ikebana) (Figure 3).



Figure 3: Ikebana or Kado

Ikebana (生け花) is the Japanese art of flower arrangement, also known as Kado (華道, the "way of flowers"). It is one of the traditional arts that has been practiced for more than 600 years. More than simply putting flowers in a container, Ikebana is a disciplined art form in which nature and humanity are brought together.

At age 74 years, she had difficulty preparing syringes and injections for vaccinations for community residents. At 75 years old, a public health nurse noted that she reported that the taste of her cooking had changed, although she had a score of 30 on the Mini-Mental State Examination (MMSE), which grades the cognitive state of patients [4]. The next year, her neighbors saw signs of amnesia; however, she was still able to teach flower arranging at her school. At times, she displayed persecution delusions.

At age 77, her MMSE score had decreased to 7 due to severe aphasia and constructional disturbance. She showed severe anomia and agraphia with relative sparing in repetition and comprehension of single words. In the community, she did not understand how to use Japanese coins. When she was 79 years old, her MMSE score had decreased to 2 due to severe jargon aphasia, and she was admitted to a nursing home. Alzheimer disease (AD) was diagnosed based on the NINCDS-ADRDA criteria [5].

After donepezil treatment, the patient received psychosocial intervention using reminiscence therapy, reality orientation, and art therapy, supported by ikebana. Each psychosocial intervention is described below. At the start of the intervention, reality orientation was performed with a focus on seasonal orientation in relation to the flowers used in arrangements. The patient was then asked about the names of these flowers. Her life history as a professor of ikebana was also used in reminiscence therapy. One of the authors, a clinical nurse specialist who is also a professor of ikebana, supported this intervention. The intervention took place for 1 hour, once a week for 12 months.

Positron emission tomography (PET) was performed to investigate possible neural outcomes of the comprehensive intervention. Cerebral glucose metabolism (CMRglc) was measured at baseline, in the middle of the intervention period (6 months), and after the intervention (12 months), as the best measure of neuronal activity.

The clinical course of the patient after the comprehensive intervention was as follows.

At 1 month, the patient's face lit up when she saw the flowers. Despite her jargon aphasia before the intervention, she spoke a meaningful sentence for the first time in several years. She was able to discriminate Japanese flowers from Western flowers, and did not want them to be mixed by the therapist.

At 4 months, the patient spoke the word *natto* ('fermented soybeans' in Japan), probably because the shape or smell of the flowers was similar to that of *natto*. After administration of a small dose of donepezil (3 mg/day), she became active and said, 'Let's do some flower arranging!' She was able to cut flowers with scissors by herself. Assistance with changing the patient's clothes or giving her a bath required less time than before treatment (reduced from 30 minutes to 10 minutes). She became aggressive when the dose of donepezil was increased to 5 mg/day, and thus the smaller dose of 3 mg/day was used for 7 months from the start of intervention; after which a dose of 5 mg/day was administered.

At 9 months, the patient was able to point to a bell flower and told staff, 'it was in bloom in my garden.' She talked like a professor of ikebana and thought of the staff members as her students. She could communicate with the nursing staff and could sing an original song in which she portrayed herself as 'foolish'.

At 11 months, she could recall past days and could point to herself in a photo taken when she was in her 30s. She asked a therapist to cut the flowers by just saying 'it is good,' and became restless. She did not pay much attention to the flowers, and sang a song. The sessions came to an end.

Regarding metabolic findings, the mean grey matter CMRglc values were 5.25, 5.21, and 3.51 mg/100 ml/min at baseline, in the middle of the study period, and after the intervention, respectively. Glucose metabolism in the middle of the study period was about the same as that at baseline, but regional CMRglc in the thalamus and medial frontal lobe was apparently stimulated, indicating that the thalamus and frontocortical network were stimulated after the combined therapy. All regional CMRglc values decreased after the intervention was ended.

After the patient's attention function was stimulated by donepezil administration, preserved functions may have been stimulated by psychosocial intervention. Clinically, patients with AD who manifest recent memory deficit can have intact remote memory and retain their skills. The psychosocial intervention program was designed to align with her remote memories and skills, based on her life history. Good emotional relationships between patients and staff, as shown by high participation rates, can enhance the positive effect of an intervention. In this case, the patient participated in reminiscence therapy supported by ikebana, in which she had experience and was a licensed professor, as was the therapist.

2.2. Neurological background

The neural mechanism requires discussion. Single photon emission computerized tomography (SPECT) studies have shown that donepezil treatment preserves global cerebral blood flow (CBF) [6] or regional CBF in the bilateral anterior cingulate and right prefrontal lobe [7]. Using PET, Tune et al. [8] performed a 24-week randomized, double-blind study to examine the effect of donepezil on CMRglc. At 24 weeks, the mean CMRglc was within 0.5% of baseline levels for donepezil-treated patients. Significant treatment differences showing the efficacy of donepezil on regional CMRglc occurred in the right frontal, right parietal, left frontal, and left temporal lobes.

The ascending cholinergic cortical projection from the nucleus basalis of Meynert plays a central role in attention function, especially in tasks of divided, cross-modal, or sustained attention [9]. After administration of donepezil, the level of acetylcholine is increased, and thus, attention function may be stimulated. Psychosocial interventions (aligned with life histories or hobbies of patients) can enhance stimulation of attention function by donepezil [10,11].

The pathology of AD involves changes in the posterior cingulate, medial temporal lobe, and limbic structures, followed by the association neocortices [12,13]. The fronto subcortical network is usually intact in AD and may be functionally active. Previous studies have not detected changes in thalamic CBF or glucose metabolism. Since the thalamus is associated with sensory function, psychosocial intervention may stimulate sensory function and activate thalamo cortical circuits along with frontal stimulation by donepezil. A schematic representation is illustrated in **Figure 4**.

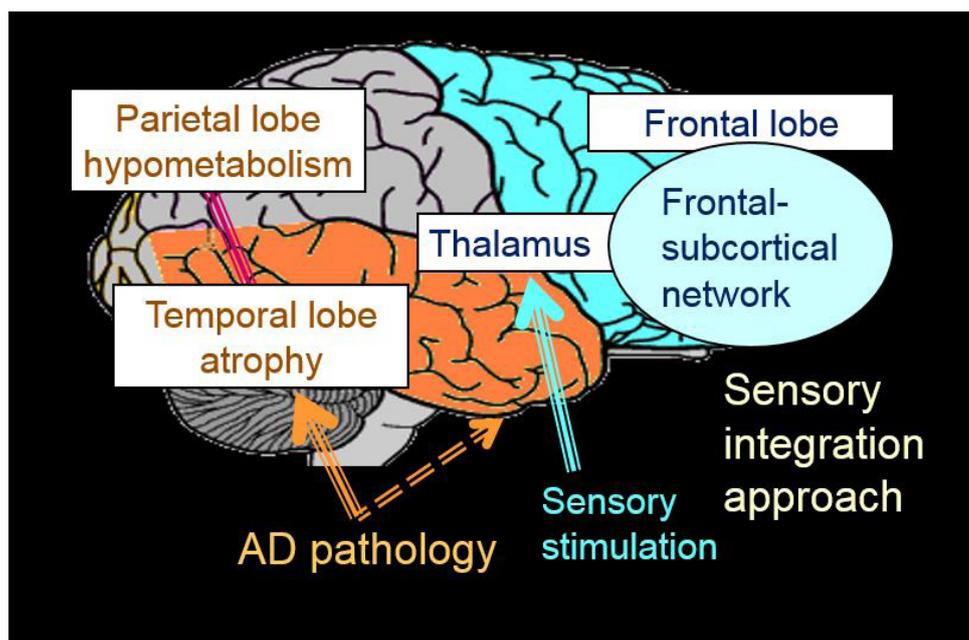


Figure 4: Neural background of sensory integration approach for AD

3. Group Reminiscence with Realty Orientation

Reminiscence therapy seeks to facilitate the recall of past experiences to promote

intrapersonal and interpersonal functioning, and thereby improve well-being and QOL [14-17]. This therapy involves discussion of past activities, usually with the aid of tangible prompts such as photographs, household items, and other familiar items from the past. Relatively well-preserved remote memory in AD can provide a neurological basis to support this therapy [18]. The reality orientation technique [14,17,19] is also used as a psychosocial intervention for patients with dementia, who frequently show disorientation. In this method, orientation information, such as time and place, is presented, and this is thought to improve understanding of surroundings, and potentially promote a sense of control and self-esteem. It is usually used in combination with reminiscence therapy [19].

3.1. Group reminiscence with reality orientation

The following are scenes of group reminiscence with reality orientation, which were broadcast on television. Three such scenes are shown in **Figure 5**.



Figure 5: Group work of institutionalized Patients

- This is a nursing home in Tajiri, Miyagi Prefecture, at which we have performed group reminiscence since last year. The home has 53 older adult residents, some of whom have dementia. We wanted to be able to communicate with these residents, rather than just caring for them physically.
- Group reminiscence is performed every Thursday afternoon. Six residents and 4 staff members talk together about the old days as a group. One topic is discussed each session and we use prompts to initiate the conversation. Today's topic is marriage.
- “It is a good *furisode* with a nice color.” The kimono reminded the patients of their marriage. The staff help them to recall their memories and lead the conversation.
- “Maybe it is difficult to remember, since it was more than 50 years ago. Did you wear

shikomukuo or *wataboshi* (Japanese traditional wedding clothes)?)”

- “No I didn’t. It was not formal, just simple. It was like the wedding of a mouse.”
- In the old days they did not have enough wedding clothes. Sometimes the topic of conversation will touch on a special situation in the old days. Some residents recalled World War II.
- “I remember the war very well, but nothing about marriage, it is true. I remember that I was lucky not to be killed in the war.”
- “My fiancée was in Manchuria, so I went by myself to get married there. Thus, I did not have a wedding ceremony.” “She went by herself to Manchuria, where her husband was working. Did you really go by yourself? So she did not have a wedding ceremony.”
- After continuing this conversation, the residents became cheerful. The staff also understood them better by listening to them carefully.
- “First, their expressions were masked. However, they became cheerful after the reminiscence approach. Since we used topics related to their old days, we are able to understand their thinking and life histories more clearly. I think this will help in our daily care for the residents.”

3.2. Evidence for the utility of group reminiscence with reality orientation

We previously evaluated the beneficial effects of group reminiscence in patients with vascular dementia (VaD), using cognitive and observed behavioral parameters [20]. Sixty patients who were diagnosed with VaD were randomly assigned to three arms: a group reminiscence approach (GRA) arm, a social contact (SC) arm, and a control (CL) arm. One-hour GRA and SC sessions were given once a week for 3 months for the GRA and SC arms, respectively, while only supportive care was given in the CL arm. Improvements in cognitive function and behavioral activities were defined as the primary outcome. However, we found no significant improvements in these measures, and we concluded that the results did not support the hypothesis that GRA is beneficial to patients with VaD.

The drop out rate was higher in the SC arm than in the GRA and CL arms. The participants in the SC arm told us that the intervention was very boring. The SC content was 50 minutes of group work to talk about social issues such as health and disease management, and hot topics from today’s newspaper; and interests in daily living, including recreation and meals in their facilities. In contrast, older residents enjoyed talking about their past memories, as in the GRA arm, and preventing this discussion by presenting social topics made them feel that the SC arm was boring.

Since we had assessed emotional ratings for the GRA and SC arms, we performed a secondary analysis [21]. Five ratings of “very enjoyable,” “enjoyable,” “normal,” “boring,” and “very boring” were used. For the GRA arm, 76% of subjects answered very enjoyable or enjoyable, whereas only 27% gave these answers for the SC arm. We classified the subjects into the “Enjoyable” and “Boring” groups, independent of the contents of the GRA or SC, and we found that the “Enjoyable” group had a significant improvement on the MOSES scale compared with the “Boring” group.

We previously reported a case of a patient with dementia with improvement of their mental inner world after a psychosocial approach, despite there being no marked change in MMSE score [3]. In contrast to clinical trials of drugs, psychosocial approaches may not be appropriate for a RCT design, and caution is required regarding “superficial” interpretation. Instead, a patient-reported outcome (PRO) [21] may be more important for a psychosocial intervention.

4. Cooking

Patients with AD often have eating disorders. Hospitals and nursing homes usually provide liquid foods for such patients, but their appetite and QOL do not always improve. Food is both a nutritional (biological) and cultural (psycho-socio-spiritual) issue. Traditional Japanese food is based on the cosmic dual forces (*in*, negative; and *yo*, positive) and the five elements (wood, fire, earth, metal and water) in oriental cosmology. This food tastes of, and also represents, the seasons through visual sensation, and thus can be used as a part of a psychosocial intervention.

4.1. Case report

We reported [22] a mild AD case in which depressive mood and decreased daily activity improved markedly after consumption of traditional Japanese food. The patient was an 80-year-old, right-handed woman who had worked as a farmer for a long time. Her depressive mood became apparent over several years and an antidepressant was prescribed by her doctor; however, this was ineffective. She became almost completely bedridden. ECD-SPECT (**Figure 6, 1st eZIS**) revealed decreased frontal CBF, which was consistent with her depressive state.

A psychologist initiated a psychosocial intervention using traditional Japanese food once a day for two months. A reality orientation with reminiscence was combined with this approach. The drug treatment was unchanged throughout the intervention. After the 2-month intervention, her depressive state and decreased ADL improved markedly, and she became able to walk by herself. A second ECD-SPECT (**Figure 6, 2nd eZIS**) showed that frontal CBF had almost returned to a normal level. These results suggest that traditional Japanese food may be an effective psychosocial intervention for patients with MCI.

We used eZIS developed by Matsuda et al. [23], which is based on the idea of SPM (eZIS is an automatic and Matlab® free version of SPM). Using voxel-based spatial normalization, a SPECT image of one subject was converted into the same stereotaxic space as normal age-matched database images. Voxel-wise z-scores $\{[(\text{CBF of patient}) - (\text{CBF of normal database})] / (\text{SR})\}$ were computed, and voxels with a supra-threshold ($p < 0.05$) were detected as significant areas.

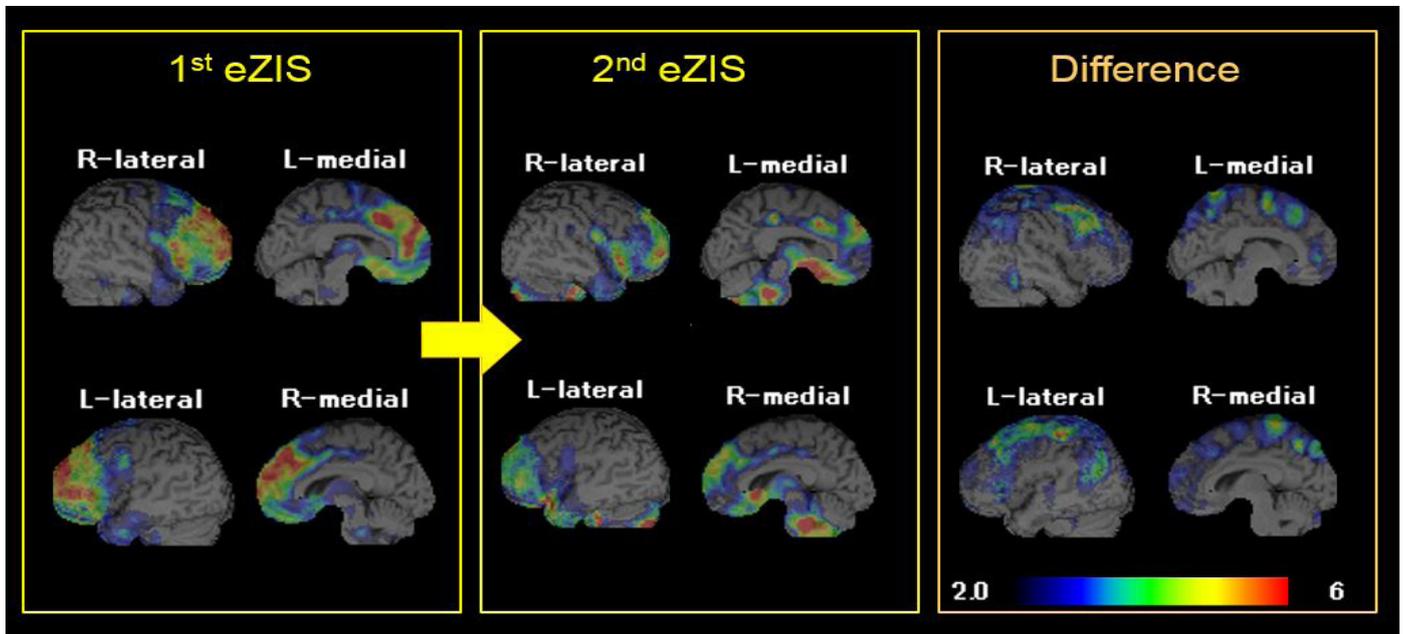


Figure 6: ECD-SPECT Results

4.2. Group work for cooking

Group work for cooking was also performed, as illustrated in **Figure 7**. Patients made traditional Japanese food supervised by an occupational therapist and a dietician. After cooking, they ate with families. One PRO was that “it was delicious, especially eating with other people.” After 30 min, the patients were shown the dishes that they had made, but they did not remember due to memory impairment of AD. However, during cooking, they had happy faces, which suggests improved QOL.



Figure 7: Group Work for out patients for AD Cooking With Families Intervention by a occupational therapist and a dietician

5. Art Therapy

Art therapy [24] is also a potential component of combined therapy. AD has an impact on creativity, but patients may be able to produce art with a focus on color and composition, and this can help with identifying the strengths of patients with AD [25].

5.1. Calligraphy

Calligraphy is widely practiced and revered in East Asian countries that use or used Kanji, and it is good for meditation. There is a general standardization of the various styles of calligraphy in the East Asian tradition. Group work was supervised by a speech pathologist and a public health nurse, as illustrated in **Figure 8**. One spontaneous PRO was “Happiness lies in my mind”.



A patients (CDR 1) spontaneously wrote “Happiness lies in my mind.”

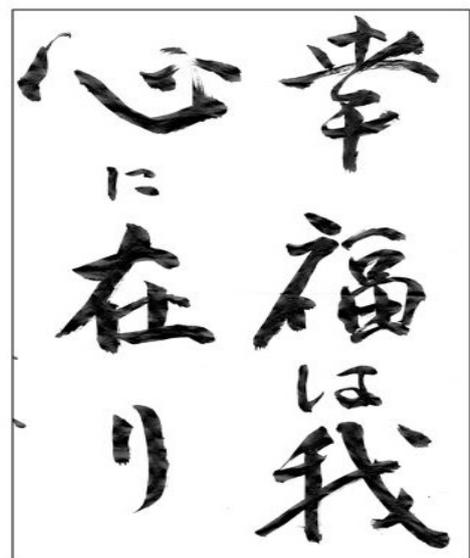


Figure 8: Group Work for out patients with AD Calligraphy Intervention by a speech pathologist and a public health nurse

5.2. Collage activity: Spiritual presentation?

Collage is well known as a unique technique of modern art. In academic history, it was first introduced as a method for assessing the psychodynamics of psychiatric patients [26], and it has become popular in art therapy [27]. Collage is sometimes used in psychosocial interventions for patients with AD as a creative and recreational activity [28]. As psychological support for elderly patients with dementia, Holden et al. [29] noted “these can be made in the group; members search through magazines looking for pictures that illustrate the particular theme, cut these out and stick them on a large piece of paper (pg. 159-160)”.

Collage activities have become popular among therapists working on dementia in Western countries, but the outcomes of resulting articles have not been analyzed in full. In Japan, the collage technique was introduced as psychotherapeutic “collage therapy” in the late 1980s, and has since been applied in illnesses such as neurosis, depression, and schizophrenia [30].

In Japanese reports, therapists have generally interpreted collages in terms of the framework of projective or symbolic theory.

We studied 20 patients with AD [31], who were asked to select and place several clippings in any manner they wished. The pieces had been cut from old magazines by the patients when their symptoms were relatively mild. The pieces were placed in a box by therapists. Many patients showed a tendency to simplify; i.e., they cut several pieces into squares and placed them parallel to one another on the sheet of paper.

A collage made by an 82-year-old woman with a MMSE score of 23 is shown in **Figure 9**. The main items were the sunrise or sunset and an image of Buddha, which were thought to reflect a simple spiritual theme. Butler [32] noted that, “old age inaugurated the process of the life review, promoted by the realization of approaching dissolution and death” (pg.534). These processes may be promoted by awareness of the disease in the early stage in AD patients. Intriguingly, the spiritual theme was not generally discussed in conversations with patients, but did appear in their collages.

In the last decade, there have been more studies of the internal aspects of dementia. Sabat et al. [33] reported a detailed discourse of conversations with AD patients and emphasized that a sense of self was intact in their world, and that some patients were still aware of their deficits, even in the severe disease stage. Bender et al. [34] noted that psychologists should understand the subjective world of patients with dementia and that use of various psychotherapeutic methods was necessary. Holden et al. [29] described psychological interventions as an integrated care approach for dementia, and Clare et al. [35] discussed the possibility of cognitive rehabilitation in dementia. Moreover, Coleman et al. [36] discussed the significance of the spiritual aspect in care. All these arguments can be interpreted as an attempt to construct a more holistic perspective for dementia. We believe that collage therapy, as a psychological technique, can contribute to this new perspective for patients with dementia by exploring messages from their inner world.



Figure 9: Spiritual image

6. Evidence for use of a Comprehensive Approach

6.1. QOL as an outcome

We have examined the combined effect of donepezil and psychosocial intervention on cognitive function and QOL for patients with AD [37]. who received donepezil with or without the various psychosocial interventions described above. We found that there was no group effect for MMSE changes, but a significant group effect with a time by group interaction for QOL-AD changes.

6.2. Neurological background

We have previously reported that the frontal lobe is stimulated by psychosocial intervention in patients with dementia [38], and that the parietal lobe is associated with logical judgment [39]. We hypothesized that a combined approach with symptomatic drug treatment can directly stimulate attention function and affect judgment function indirectly through observing behaviors of other subjects. Fifty-two patients with AD under went group reminiscence with reality orientation, as well as donepezil treatment [11]. CBF was assessed with ECD SPECT. Two analyses were performed: comparison of responders vs. non-responders based on MMSE scores, and comparison of those with good vs. poor memory of the intervention content. CBF in the frontal lobe was significantly higher in responders (vs. non-responders), and CBF in the parietal lobe, especially on the left side, was significantly higher in those with a good (vs. poor) memory. Donepezil directly stimulated areas similar to those affected by the psychosocial intervention, suggesting that the drug was compatible with the intervention. The parietal lobe was stimulated indirectly, suggesting that the indirect effect of the intervention may be based on logical judgment function.

7. Long-Term Effect: QALY

7.1. Combined effect of drug and psychosocial intervention

Cholinesterase inhibitors such as donepezil delay progression of AD, but their effect on life expectancy is unclear. We analyzed the influence of donepezil on life expectancy after onset of AD, together with the effects of antipsychotic drugs and residency in a nursing home [40]. All out patients at the Tajiri Clinic from 1999-2012 with available medical records and death certificates were included in a retrospective analysis. The entry criteria were a dementia diagnosis based on DSM-IV criteria and diagnosis of AD using NINCDS-ADRDA criteria; medical treatment for >3 months; and follow up until <1 year before death. Of 390 subjects with medical records and death certificates, 275 had a diagnosis of dementia that met the entry criteria. Of 100 patients diagnosed with AD, 52 had taken donepezil and 48 had not received the drug (due to treatment prior to introduction of donepezil in 1999 in Japan). The life expectancies after onset were 7.9 and 5.3 years in these respective groups. There was a

significant drug effect with a significant covariate effect of nursing home residency. Other covariates did not reach a significant level.

This report has the limitation of all retrospective studies of a lack of randomization, but we found a positive effect of donepezil on life expectancy after onset of AD. This may be due to decreased mortality caused by reduction of concomitant diseases such as pneumonia. The similar life expectancies inpatients taking donepezil at home and those not taking donepezil in a nursing home indicated a positive health economic effect of the drug.

7.2. Effect of cerebrovascular diseases

The positive effects found above for nursing home residence and donepezil administration on life expectancy after onset of AD did not include the effect on quality-adjusted life-year (QALY) or the impact of concomitant cerebrovascular disease (CVD). Based upon our recently reported health state utility values, we analyzed these effects in patients with ‘pure’ AD (without CVD) or AD with CVD [41].

A retrospective analysis was performed in all out patients at the Tajiri Clinic from 1999-2012 with available medical records and death certificates. The entry criteria were a dementia diagnosis based on DSM-IV and a diagnosis of pure AD or AD with CVD using NINCDS-ADRDA, medical treatment for >3 months, and follow up to <1 year before death. The main outcomes were life expectancy (months between onset of dementia and death) and QALY.

Of 390 subjects, 275 had a diagnosis of dementia that met the entry criteria, including 67 with pure AD, 33 with AD and CVD, and 110 with VaD. Of the AD patients, 52 had taken donepezil and 48 had not received the drug, as described above. In the pure AD group, there were positive effects of nursing home residence and donepezil on QALY, as well as on life expectancy. In the AD with CVD group, donepezil only had an effect on life expectancy, with no effect on QALY.

Within the limitation of lack of randomization, we found positive effects of donepezil and nursing home residence on life expectancy and QALY after onset of AD, which may be due to decreased mortality, as described above. However, concomitant CVD negated this positive effect on QALY. These findings suggest that QALY in AD is affected by CVD, which indicates the importance of CVD prevention in patients with AD.

8. Highlights

- ◆ We report a case of Alzheimer disease (AD) in which a combined approach using donepezil and psycho social interventions was effective for improving cognitive maintenance and quality of life (QOL). Fluorodeoxyglucose (FDG)-positron emission tomography (PET) revealed stimulation of glucose metabolism in the thalamus and fronto-subcortical network.
- ◆ Treatment effects on cognitive function and QOL were investigated in groups treated with donepezil with or without psychosocial intervention. There was no group effect for Mini-Mental State Examination (MMSE) changes, but a significant group effect for QOL-AD changes.
- ◆ The combination treatment provided new perspectives for patients with dementia by exploring messages from their inner world, especially from a spiritual perspective and for QOL.
- ◆ The combined approach stimulated attention function directly, as revealed by an increase in frontal cerebral blood flow (CBF), and judgment function indirectly, based on observing behaviors of other participants and increased parietal CBF.
- ◆ Regarding the long-term effect, we found a positive effect of the combined approach on life expectancy adjusted for QOL (QALY) after onset of AD.

9. References

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