

Editorial

Non-pharmacological intervention for dementia patients

OWING TO THE prolonged average life span of human beings since the 19th century, the ratio of the elderly population in the world has rapidly increased, and it will continue to increase, especially in developing regions, including Asia. One consequence of increased longevity is the growing prevalence of dementia in these regions, especially in Asia.¹ In the year 2005, there were 13.7 million dementia patients in the Asian region (5.5 million in China, 3.2 million in India, and 1.9 million in Japan) and this number is expected to increase to 64.6 million (27.0 million in China, 16.3 million in India, and 4.9 million in Japan) by the year 2050.¹ Reflecting the faster increase of the elderly population in developing countries, more dementia patients will be observed in Asia, and in other developing countries, than in developed countries in the near future.²

Donepezil, a choline esterase inhibitor, was developed and approved in Japan in November 1999, and it has been the only drug for Alzheimer's disease available in Japan for 12 years. This year (2011), three new compounds (galantamine, rivastigmine, and memantine) have been approved for Alzheimer's disease by the Japanese Government, which has provided alternatives for patients.³ Even though all of these drugs, including donepezil, are only symptomatic,⁴ the possibility of a choice of drugs is certainly favorably accepted by patients and doctors. These drugs will not cure Alzheimer's disease, leaving a similar or even higher number of patients to be treated.

Recognizing the limited benefits of the symptomatic drugs, the development of the disease-modifying drug for Alzheimer's disease is the urgent target for research laboratories and pharmaceutical companies.⁵ There are more than 100 compounds searched for and considered for the disease-modifying drug, and some compounds have successfully undergone pre-clinical studies and have been put forward to clinical trials; however, all compounds tested in clinical trials for Alzheimer's disease have failed to demonstrate clinical usefulness in the past 2 decades.

The list of unsuccessful compounds evaluated in clinical trials for Alzheimer's disease includes

AN1792 amyloid vaccine (Elan, 1992), atorvastatin (HMG CoA reductase inhibitor, Pfizer), simvastatin (drug for hyperlipidemia, Banyu), Dimebon (anti-histaminergic drug, Pfizer, 2010), Ginkgo biloba (mitochondrial membrane stabilization, and anti-oxidant effect), tarenflurbil (non-steroidal anti-inflammatory drug, gamma-secretase modulator, Myriad, 2009), phenserine (choline esterase inhibitor, amyloid-beta production inhibitor), rosiglitazone (anti-diabetes drug, insulin resistance, Glaxo-Smith-Kline), tramiprosate (amyloid-beta aggregation inhibitor, Neurochem, 2007), and xaliproden (5-HT_{1A} agonist for amyotrophic lateral sclerosis).

After paying a huge loss of labor, time, and money, researchers are still struggling to determine the reasons for the consecutive failures in developing the disease-modifying drugs for Alzheimer's disease, discussing the discrepancy between animal studies and human clinical trials, the measure of efficacy evaluation in clinical trials, and the validity of the amyloid cascade hypothesis. Considering the difficulty of developing new drugs for Alzheimer's disease, it might be time to think over the possibility of treatment from broader perspectives.^{6–8} In this article, complementary and alternative medicine (CAM) for Alzheimer's disease will be briefly reviewed⁹ and the present state of non-pharmacological treatment will be discussed.

SOCIAL ASPECT OF DEMENTIA

Dementia is a syndrome associated with a progressive loss of memory and cognitive functions that is serious enough to interfere with performing the tasks of daily life. The loss of memory and cognitive function is caused by a variety of disorders, most commonly in the elderly by neurodegenerative disorders, including Alzheimer's disease. Dementia can occur to anyone at any age from an injury or from oxygen deprivation, although it is most commonly associated with aging. It is the leading cause of institutionalization of the elderly. Along with the progression of cognitive impairment due to dementia, the capacity of performing the tasks of daily life is deteriorated. As shown in Figure 1, complex social life capacity is

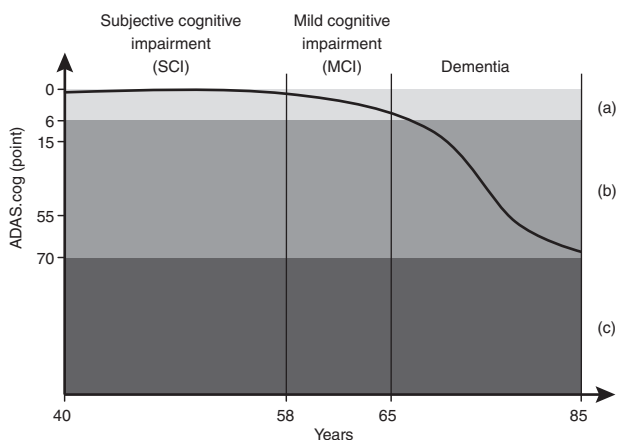


Figure 1. Most people notice memory decline when they become 40 years old on average (subjective cognitive impairment [SCI]), in which the whole capacity including social life, personal life, and biological life are preserved. Some may show mild cognitive impairment (MCI), in which social life capacity is impaired. In dementia stage, social life capacity and personal life capacity are impaired but the biological life capacity is preserved.

(a) Social life capacity. (b) Personal life capacity. (c) Biological life capacity.

gradually deteriorated due to memory impairment during subjective cognitive impairment (SCI) and mild cognitive impairment (MCI) stages, even before the clinical diagnosis of dementia. When the diagnosis of dementia is given, the patient is no more able to function in social life, and their personal capacity will further deteriorate with the progression of the disease; however the biological life capacity will be maintained until the end of life (Fig. 1).

The tasks of daily life are different for each individual, and the timing of diagnosis of dementia may depend on the previous social and occupational complexity of the patient's daily life. If a patient has higher premorbid intellectual function, it is usual that the patient is not diagnosed as having dementia, even though the pathological process in the brain is far advanced, because the patient usually shows a score higher than the cut-off value of a screening test like the Mini Mental State Examination.⁹ In this respect, even the diagnosis of dementia is influenced by social factors,¹⁰ including premorbid IQ, level of education, occupation, and complexity of daily life.⁶

The symptoms of Alzheimer's disease differ for each individual patient. At the onset of dementia in some patients, certain personality traits that had been

well controlled in the past become accentuated, whereas in others there is a 'loss of personality', where the uniqueness of the patient's personality is lost. Some patients show a more rapid deterioration of cognitive function, whereas others show a slower rate of cognitive decline. Some patients exhibit various types of behavioral and psychological symptoms of dementia (BPSD), whereas others exhibit few abnormal behaviors. Furthermore, the physical, personal, familial, economic, and social environments differ between patients. Thus, each patient should be evaluated as an individual in terms of the needs for intervention, taking into account previous social functioning, family structure, and the patient's living environment in order to deliver the most appropriate care. Interventions for dementia patients need to be individualized further, taking into consideration the different genetic, environmental, and social factors that are specific to each patient.^{11–14}

CAM FOR DEMENTIA

Although modern medical science has enabled correct diagnoses to be made and proper treatments to be initiated for acute diseases caused by exogenous pathogenic factors, there are still numerous chronic, incurable diseases caused by endogenous factors, such as dementia, cancer, hypertension, diabetes, chronic pain etc., for which there is no effective treatment, leaving patients with these conditions to suffer. To facilitate the better management of these chronic diseases, recent attention has focused on the use of CAM, together with Oriental and traditional medicines^{1,9,14,15} and non-pharmacological intervention.¹² CAM is defined by the American Cancer Society as '... supportive methods used to complement evidence-based treatment. Complementary therapies do not replace mainstream treatment and are not promoted to cure disease. Rather, they control symptoms and improve well-being and quality of life.' In contrast, alternative therapies, or alternative medicine, involve non-mainstream treatments that are sometimes used by patients instead of orthodox treatments.

Reflecting the lack of effective medicine to cure most of dementia, including Alzheimer's disease, a variety of CAM are applied without supporting evidences.¹⁶ Since the symptoms of dementia (even the diagnosis, as mentioned above) are influenced by the social factors of each patient, the effectiveness of CAM is not guaranteed to all of the patients. Some

CAM are effective for some patients, but the same CAM is not effective for other patients. There are scarce data of the effectiveness of CAM and their usefulness with scientifically verified statistical analysis, which could be one of the reasons why so many different kinds of CAM are tried in public.¹⁷

CAM for dementia include off-label-use of drugs, Chinese herbal medicine, natural supplements, food, exercise, leisure activities, lifestyle, and non-pharmacological interventions. Examples of off-label use of approved drugs (alternative medicine) for dementia are Ginkgo biloba, acetyl-L-carnitine, lecithin, piracetam, curcumin, vinpocetine, phosphatidylserine, and others.¹⁸

In Asian countries, Chinese herbs are traditionally used for dementia and other medical conditions, from which active components are extracted for the treatment of dementia. Due space limitations, only the popular examples are briefly described below. Galantamine is originally extracted from *Galanthus woronowii*, a plant of the Amaryllidaceae family, and is now approved as the drug for Alzheimer's disease, marketed worldwide by Janssen Pharmaceuticals.¹⁹ Ginkgo biloba leaf preparations have been marketed in Germany and France for 30 years for the treatment of cardiovascular disease, cerebrovascular disease and dementia, and are sold as natural supplements in the USA and other countries. Huperzin A is an extract from *Huperzia serrata* (Qian Ceng Ta) for its potent acetylcholine esterase inhibitor action. Huperzine A is widely used as an effective cognitive enhancer for dementia patients in China and in other countries.²⁰ Ginsenosides extracted from Panax ginseng are shown to improve learning and memory function through the mechanism of increasing acetylcholine level and also density of muscarinic recep-

tors.²¹ Ursolic acid extracted from *Salvia officinalis* is shown to have neuroprotective effects and inhibit acetylcholine esterase *in vitro*, showing memory improvement in clinical study. Epigallocatechin-3-gallate is the active component of green tea, a popular daily drink for Asian people, which has shown to have neuroprotective and antioxidative activity. Curcumin, an extract from the Curcuma root, is shown to be effective for improving learning and memory, which is also shown to decrease amyloid-beta by gamma-secretase inhibitor activity. Clausenamide, a major component of aqueous extract from the leaves of *Clausena lansium*, has been under study as a promising candidate for dementia treatment. The list of the compounds extracted from Chinese herbs is growing, and these are only some examples of the compounds that can be developed for drugs for dementia. A more complete list is available in the literature.²²

NON-PHARMACOLOGICAL INTERVENTION FOR ALZHEIMER'S DISEASE

Four drugs (donepezil, rivastigmine, galantamine, and memantine) are now available in Japan and many other countries. The benefits for patients treated with one of these drugs (some are treated with a combination of acetylcholine esterase inhibitor and N-Methyl-D-aspartate antagonist) are not satisfactory. Even though the treated patient may show some cognitive improvement for several months, they show a similar level of cognitive function after 1 year or so, showing the same rate of cognitive decline as untreated patients (Fig. 2).

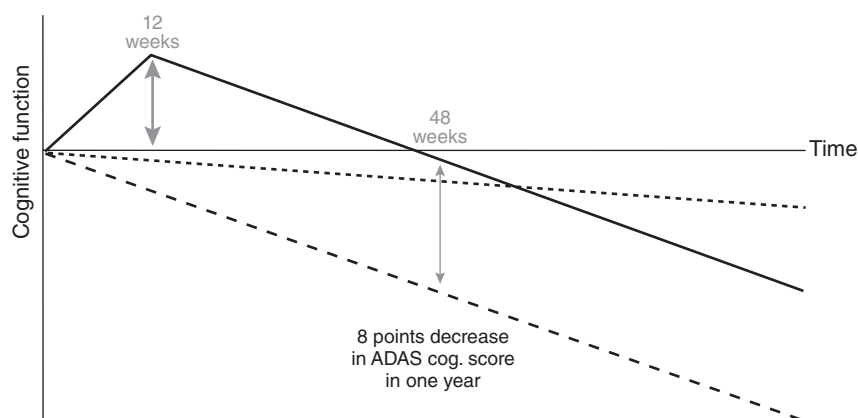


Figure 2. Broken line (– –) shows natural course of cognitive decline with dementia patients. Solid line (—) shows the cognitive function of the patients treated with symptomatic drugs such as AChE inhibitors. Short broken line (---) represents the cognitive decline of the patients treated with disease-modifying drugs.

Table 1. Non-pharmacological intervention to Alzheimer patients

Therapy	Cognitive	ADL	BPSD
Cognitive training	+	+	+
Cognitive rehabilitation	+	+	+
Cognitive stimulation therapy	+	+	+
Snoezelen/multisensory stimulation	+	+	+
Reality orientation	+	+	+
Reminiscence therapy	+	–	+
Validation therapy	+	–	+
Physical activity	+	+	+
Light therapy	+	–	+
Music therapy	+	–	+
Aromatherapy	–	–	+
Animal-assisted therapy	–	–	+

ADL, activities of daily living; BPSD, behavioral and psychological symptoms of dementia.

Patients, caregivers, and medical professionals have been searching for an effective intervention for Alzheimer's disease, and there are a variety of non-pharmacological interventions commonly applied to Alzheimer patients. The limited efficacy of drug therapy and the plasticity of the human brain are the two main reasons that explain this growing interest in non-pharmacological intervention for dementia patients. In Table 1, non-pharmacological interventions are listed with the positive results of published randomized controlled trials (RCT) that have targeted at least one of the symptoms of dementia. The symptoms are grouped under three headings: cognitive function, activities of daily living (ADL), and BPSD. Some popular non-pharmacological interventions are discussed in the frame of two main approaches: cognitive approaches, multi-strategy approaches (reality orientation, reminiscence therapy and validation therapy), and miscellaneous approaches (Table 1).

COGNITIVE TRAINING, COGNITIVE REHABILITATION, COGNITIVE STIMULATION THERAPY

Cognitive training has been frequently mislabeled or conflated with other ill-defined therapies, such as cognitive rehabilitation, and cognitive stimulation therapy. Cognitive training is defined as the structured practice of complex mental activity in order to enhance cognitive function. An operational defini-

tion of cognitive training, delineating from other interventions, includes repeated practice, on problem activities, using standardized tasks, and target-specified cognitive domains.²³ Cognitive training can be further distinguished to include training in applied memory strategies versus repetitive cognitive exercises. Training in memory strategies involves the instruction and practice of techniques to minimize memory impairment and enhance performance, and involves learning and practicing strategies, such as the method of loci, mnemonics, and visual imagery. In contrast, cognitive exercise requires the repeated practice of targeted cognitive abilities in a repetitions-sessions format: users typically carry out a number of iterations of a cognitive task in one session, then continue to new tasks in the next session, and eventually return to further train the original task at a harder level in future sessions (i.e., staircase design). Recently, several software applications have been developed that implement cognitive exercises on computer.

There is evidence from a modest number of well-conducted RCT that cognitive training, cognitive rehabilitation, and cognitive stimulation therapy confer modest but significant benefits in the treatment of cognitive symptoms of Alzheimer patients. A meta-analysis of longitudinal RCT of cognitive training in cognitively healthy adults demonstrated efficacy on primary cognitive outcomes.²³

The systematic review found that cognitive training can produce moderate-to-large beneficial effects to MCI subjects on memory-related outcomes. However, the number of high-quality RCT remains low, and so further trials must be a priority.

Cognitive rehabilitation also appears to result in functional benefits in Alzheimer patients. The modest number of RCT focusing on cognitive training in Alzheimer patients is consistent with the results of larger cognitive training trials in healthy older people.

The best evidence base is for cognitive stimulation therapy, although this approach is labor-intensive, and requires further evaluation of cost-effectiveness. There is currently no evidence that brain-training games provide any significant benefit to people with Alzheimer's disease.²⁴

SNOEZELLEN/MULTI-SENSORY STIMULATION

The concept of Snoezelen was originally developed in the late 1970s by Dutch therapists, Jan Hulsegge

and Ad Verheul as therapy for children with autism and other learning disabilities. Snoezelen or multi-sensory stimulation (MSS) is visual, auditory, tactile, and olfactory stimulation offered to people in a specially designed room, which relates to the interdependence of both the space (the physical environment) and the 'client-centered' approach of the practitioner (the human environment). This specially designed sensory physical environment, together with the input of the 'enabling practitioner' initiates changes in arousal by affecting the relaxation process, which aims to maximize a person's potential to focus on his own free will and to engage on a motivational stimulus, and thereby to improve communication and functioning. The clinical application of Snoezelen has been extended from the field of learning disability to dementia care over the past decade. The rationale for its use lies in providing a sensory environment that places fewer demands on intellectual abilities but capitalizes on the residual sensorimotor abilities of people with dementia. Practitioners are keen to use Snoezelen in dementia care, and some encouraging results have been documented in the area of promoting adaptive behaviors. Positive results were reported across a range of behaviors, including a reduction in apathy in people in the later stage of dementia from two RCT. In a Cochrane database review published in 2002, only two trials were reviewed and no firm conclusion was reached, even though both studies examined the short-term values of Snoezelen on people with dementia.²⁵

REALITY ORIENTATION

Alzheimer's disease patients may withdraw from contact with others and the environment as they become increasingly disoriented, which results in a lack of sensory stimulation. To prevent this understimulation from sensory inputs, 'reality orientation' was developed. It is based on the belief that continually and repeatedly telling or showing certain reminders to people with mild-to-moderate memory loss will result in an increase in interaction with others and improved orientation. This in turn can improve self-esteem and reduce problem behaviors.

Reality orientation can be taught to caregivers and family members; it can be performed in the home and should be structured around the area in which the patient spends most of his or her time. For

example, access to a window is recommended to facilitate orientation to the time of day and the weather. Other than the environmental cues, familiar objects to the patients can be used to stimulate their memory in reality orientation, such as a family scrapbooks, flash cards, Scrabble games, a globe, and large-piece jigsaw puzzles.

The effectiveness of reality orientation in dementia was evaluated by conducting a systematic literature review. This yielded 43 studies, of which, six were RCT meeting the inclusion criteria (containing 125 subjects.) Results were subjected to meta-analysis. Effects on cognition and behavior were significant in favor of treatment. The evidence indicates that reality orientation has benefits on both cognition and behavior for dementia patients. However, a continued program may be needed to sustain potential benefits.²⁶

REMINISCENCE THERAPY

Reminiscence therapy is frequently used for patients with impaired memory, paying respect to the life and experiences of the individual with the aim to help the patient maintain good mental health. In one approach, participants are guided by a trained person to reflect on a variety of aspects relating to their lives. This may be themed and centered on one period in time or it may be wider and reflect a guided discussion through an issue. The therapist may use music, photographs, replica documents, drama and sensory gardens to stimulate debate and discussion for the participants. Reminiscence therapy is believed to be useful in supporting confused patients to integrate into new living arrangements by acknowledging and respecting their life history. Reminiscence therapy is believed to promote a sense of security by reviewing comforting memories.

The effect of reality orientation was compared with reminiscence therapy for elderly people in a large residential home, using a controlled cross-over design. Both kinds of therapy group were enjoyed by both staff and residents, and enabled staff to get to know moderately and severely confused residents. The group that received reality orientation followed by reminiscence therapy showed improvement in cognitive and behavioral measures, which was not found in the other two groups. It may be important to use reality orientation techniques with dementia residents before involving them in a reminiscence group.²⁷

VALIDATION THERAPY

The validation therapy was developed by Naomi Feil in an attempt to address the shortcomings of other approaches, such as reality orientation, used with individuals who have more advanced dementia. Feil developed a model that sought to classify the stage of dementia that an individual has reached according to cognitive and behavioral signs. Its development was the result of an attempt to provide practical solutions for difficulties experienced by patients and caregivers. Important features of validation therapy include: a means of classifying behaviors; provision of simple, practical techniques that help restore dignity; prevention of deterioration into a vegetative state; provision of an empathic listener; respect and empathy for older adults with Alzheimer's disease, who are struggling to resolve unfinished business before they die; and acceptance of the person's reality.²⁸

The way in which these values are applied to provide specific interventions depends on the severity of dementia in each individual case classified into four stages: Mal orientation, Time Confusion, Repetitive Motion and Vegetation. Each stage is identified by specific cognitive and behavioral characteristics, and specific validation therapy interventions address the different cognitive and behavioral features manifested by people with dementia at each of these stages, relying upon the central 14 techniques.²⁸

Various observational studies have indicated that there are positive effects in using validation therapy in terms of the amount and duration of interactions that participants are able to make during validation groups.^{29,30} However, other studies have found no significant effects of validation therapy.³¹

OTHER NON-PHARMACOLOGICAL INTERVENTIONS

There are many other non-pharmacological interventions applied to Alzheimer patients. Physical activity, especially aerobic exercise, is believed beneficial to cognitive function, improving ADL and ameliorating some forms of BPSD. Light therapy is sometimes used to keep the circadian rhythm of dementia patients in daily life, and there are RCT reporting beneficial effects to cognitive function and BPSD. Music therapy is one of the most popular day care programs in residential care as well as day care institutions. Listening to music, singing and playing music is a popular leisure activity for dementia

patients, through which some small benefit to cognitive function is also reported. Aroma oils often gives pleasant feelings and calming effect to patients showing BPSD, especially agitation and aggression. Animal-assisted therapy is reportedly effective to reduce the BPSD of dementia patients.

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