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Review Article

Non-Pharmacologic Alternatives in the Management of Alzheimer's Disease

Elizabeth Yu-Tan[1,2], Erwin Martinez Faller[1,3], Prashant Tiwari[4]*

[1]Gradute School, Centro Escolar University, Manila, Philippines.

[2]Department of Pharmacy, University of San Carlos, Cebu City, Cebu, Philippines.

[3]Pharmacy Department, San Pedro College, Davao City, Davao del Sur, Philippines.

[4]Department of Pharmacology, College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru, Karnataka, India.

*Correspondence: cologyprashant87@gmail.com

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Abstract

Alzheimer's disease is the most common neurodegenerative disease, having complex symptoms ranging from a decline in cognitive function to dementia. This paper aims to present different non-pharmacologic methods used in the management of Alzheimer's disease as evidenced in published studies. As there is no single pathogenesis of the disease, management addresses several symptoms presented. This makes drug development challenging, and to date, there is no single effective agent to prevent or cure the disease, and management is complex. Non-pharmacologic means have been explored to possibly aid in alleviating symptoms of Alzheimer's disease. Physical activities such as yoga and exercise have shown promising results in improving cognitive function. With studies showing physical inactivity to be contributory to the risk of Alzheimer's disease, more and more research is being done to prove the beneficial gains of exercise in prevention and delay of progression of the disease. Meditation, mental imagery, music and creative expression are fun and relaxing activities with benefits for the mind. These are cost-effective means of interventions that may not only address the disease itself but other aspects of the person's well-being as well. Massage and aromatherapy are physically soothing, which release tension and calm the mind. Acupuncture has documented health benefits as it is widely used in traditional Chinese medicine. These non-pharmacologic alternatives to the management of Alzheimer's disease have been presented and practised. To increase their acceptability and to successfully integrate them into clinical practice as complementary management, more extensive evidence-based studies need to be conducted.

Keywords: Yoga and exercise; mental imagery; meditation; massage and aromatherapy

Introduction

Alzheimer's disease is the most common form of dementia [1] and the most common neurodegenerative disease wherein a decline in short-term memory and cognition that impedes daily behaviour is manifested. It has been identified that inflammation and vascular impairment influence the disease in terms of onset and progression [2]. More than one pathogenesis exists, and management is only on its symptoms. There still is no treatment for the disease [3]. A variety of initiatives have been looked into to prevent the disease occurrence, to cure it, or to arrest its progression. Immunotherapy has been explored as a possible option as the targeted-directed therapy may also have disease-modifying potential; however, this has been unsuccessful [4]. Other attempts include epigenetic modifications [5], multifunctional ligand approach [6], and targeting metal homeostasis [7], to name a few. Drug discovery and several translational research also consider these new approaches. Due to the complexity of the disease, research efforts have also moved to non-pharmacologic approaches. These

non-pharmacologic approaches provide improved functioning, which makes them promising. A review done on PubMed and the Cochrane database searches for systematic reviews on non-pharmacologic efforts and their roles in the management of Alzheimer's Disease, including exercise and motor rehabilitation, cognitive rehabilitation, complementary and alternative medicine, and some other new technology applications [8]. A published study looked into five non-pharmacological interventions, namely acupuncture, exercise, music therapy, cognitive intervention, and repetitive transcranial magnetic stimulation [9]. This shows the increasing need to search for high-quality evidence to support the use of non-pharmacologic means in the management of the disease. This chapter will present some studies done on non-pharmacologic options in the management of Alzheimer's disease, including some of the new suggestions on management to encourage more research to provide strong recommendations for the application to the disease.

A. *Yoga*

Little is known about yoga's effects on cognitive function in adults with mild cognitive impairment and dementia, despite the fact that it has been utilized to improve adult cognitive function as a supplemental therapy [10]. Yogic practices have been shown to improve the redox health of the body, which reduces complications brought about by imbalances. While more studies are still needed to validate the findings, initially, yoga has been shown to reverse memory loss [11]. A study by Krause-Sorio *et al.* on the gray matter volume changes in older women with subjective cognitive decline and cardiovascular risk factors, which are known risk factors for developing Alzheimer's Disease, showed that yoga training might offer neuroprotective effects compared to memory enhancement training. It should improve even over a short time interval done in the study [12]. Another study showed that yoga improves flexibility of mind and body and decreases anxiety, among other benefits which are favourable to patients with Alzheimer's Disease [13].

B. *Mental imagery*

In the absence of the proper external cues, mental imaging is described as a quasi-perceptual experience in the Stanford Encyclopedia of Philosophy [14]. Due to impaired visuospatial, executive, and semantic memory, it is impossible to perform the more complicated imagery. Nevertheless, using mental rehearsal and visualization as part of a multi-session rehabilitative intervention strategy can be beneficial [15].

C. *Creative expression*

Adult patients with mild cognitive impairment who were 60 years of age or older were randomly allocated to either creative treatment or standard cognitive training in the control group. There were several questionnaires utilized. Following the session, patients getting creative treatment performed noticeably better than those receiving conventional cognitive training. This affordable therapy might be used in addition to more traditional treatments [16].

D. *Massage*

A systematic review with meta-analysis looked into the application of manual massage on patients with dementia, revealed that this can be a non-pharmacologic strategy to improve behavioral and psychological symptoms [17]. A study on Shiatsu was done in search of a feasible option to address depression in Alzheimer's disease. In a single-blind study, patients with Alzheimer's disease who had depression were randomly assigned to a group that had physical activity and Shiatsu or another group that only had physical activity. The forms used to assess the participants were the Mini-Mental State Examination, Geriatric Depression Scale (GDS), Activity of Daily Living, and Instrumental Activity of Daily Living. The group that received Shiatsu and physical activity had a significant decrease in GDS scores. The decrease could have been brought about by the neuroendocrine medicated effects of Shiatsu on neural circuits that have an effect on mood and affect regulation [18].

E. *Aromatherapy*

Alzheimer's disease has some typical Behavioral and Psychological Symptoms of Dementia and relies on antipsychotic drugs for management. In the long term, they do not sustain their effectiveness and come with side effects [19]. Various studies have looked into the potential of aromatherapy in the management of Alzheimer's Disease. However, its mechanism of action remains to be elucidated. There was a study using the senescence-accelerated mouse prone 8 as a model for dementia. The Y-maze test was used to measure the mice's cognitive function before and after they were exposed to a combination of essential oils during the day and at night. Following treatment, the levels of brain-derived neurotrophic factor (BDNF), abnormally phosphorylated tau, and amyloid beta (A) were assessed. It was confirmed that aromatherapy has advantages for cognitive function [20]. A study was conducted to assess the effects of aroma oil as a bath salt on several aspects, such as cognitive function, olfactory function, and sleep quality, where they randomized 35 patients. The tools used to assess are the Touch Panel-Type Dementia Assessment Scale, the Odor Stick Identification Test for Japanese and the Japanese version of the Pittsburgh Sleep Quality Index done five times throughout the study. Cognitive performance was altered both before and after using the fragrance bath salt, and sleep-related factors were linked to these changes, suggesting that improving sleep will also improve cognitive function [21]. A study looked into the improvement of dementia symptoms by olfactory nerve stimulation. It made use of disinfecting ethanol added with aroma extracts from cedar. The evaluation was performed after 8 weeks using the Neuropsychiatric Inventory, the Japanese version of the Zarit Caregiver Burden interview, and the ADAS-cog scale. Improvement was seen in all areas except for the ADAS-cog scores. Therefore, exposure to cedar smell may lessen the need for nursing care while improving the behavioural and psychological symptoms of dementia in Alzheimer's type dementia [22].

F. *Acupuncture*

There is growing interest in looking into acupuncture's support in the management of Alzheimer's disease. A protocol to present an overview of different systematic reviews on the use of acupuncture in the disease has been published [23]. A randomized, controlled, parallel-group, exploratory study was done on patients with mild to moderate Alzheimer's disease. The AD's Assessment Scale Cognition (ADAS-Cog) scores for those who received acupuncture showed a lowering in the follow-up week compared to those who received Donepezil. The Clinician's Interview-Based Impression of Change-Plus (CIBIC-Plus) values were much lower in the acupuncture group during treatment and follow-up phases than in the group that received Donepezil [24]. Mild cognitive impairment (MCI) is considered the borderline between cognitive changes of ageing and very early Alzheimer's disease. Interventions are best done when symptoms of MCI are evident to prevent progression to Alzheimer's disease. The tools used in the study are the Korean versions of ADAS-cog, Montreal Cognitive Assessment Scale, Activation of Daily Living Scale, and Instrument Activities of Daily Living Scale. Original versions of the Center for Epidemiological Studies-Depression Scale and European Quality of Life 5 Dimension Five Level Scale were used. All groups received essential acupuncture, but in addition, specific groups received acupoint specificity, needle duration, or electroacupuncture. Upon completion of the study in 20 weeks, the group that received basic acupuncture only showed significant improvement in cognitive functions compared to other groups that received additional therapy [25].

A study protocol was designed to look into electroacupuncture for cognitive function in Alzheimer's disease. By randomization, 344 participants with the disease will be assigned to either an electroacupuncture combined with Donepezil group or Donepezil alone (1:1). The study hopes to see a change in the total score of ADAS-cog at 12 weeks [26].

Another study protocol is a randomized patient-assessor blind sham-controlled trial to assess whether electroacupuncture as an intervention will decrease the rate of cognitive decline among older adults with mild cognitive impairment. Seventy-five patients will be recruited and randomly assigned to either the group to receive electroacupuncture or to the sham group (which will have the needles as in acupuncture but without the current) [27].

It is said that acupuncture treats nervous system diseases by increasing the brain-derived neurotrophic factor level and involves multiple signal pathways [28]. A study that used functional MRI

to confirm the scientific proof of acupuncture's neuronal specificity. Siguan (four gates) produced widespread activations and deactivations in the basal ganglia, cerebellum, visual, sensorimotor, and cognitive-related regions. Actual acupuncture locations led to more significant modifications in the brain as shown in Figure 1 [29].

G. *Music and Meditation*

A pilot study was done on patients with Alzheimer's disease and their caregivers. It looked into an 8-week meditation program and its effect on perceived stress, mood, and related outcomes. Adherence was good, and outcomes were improved also based on the Perceived Stress Scale, General Sleep Disturbance Scale, Profile of Mood States, and Memory Functioning Questionnaire [30]. A study with about the same assessment parameters but evaluated Kirtan Kriya Meditation (KK) and Music Learning (ML) as interventions. After 3 months, the KK group shows more significant gains in perceived stress, mood, psychological well-being, and QOP-Mental Health. Sustained gains and continuous improvement were seen for up to 6 months [31]. The same interventions applied evaluated 53 participants. The tools used to assess were the memory functioning questionnaire, trail-making test, and Digit-symbol substitution test. Both groups showed marked and significant improvement at 3 months in their memory and cognitive performance [32]. Another study from the same research team looked into telomere length and telomerase activity in addition to stress, mood, and quality of life parameters. The group exposed to KK had better outcomes compared to the ML group [33, 34].

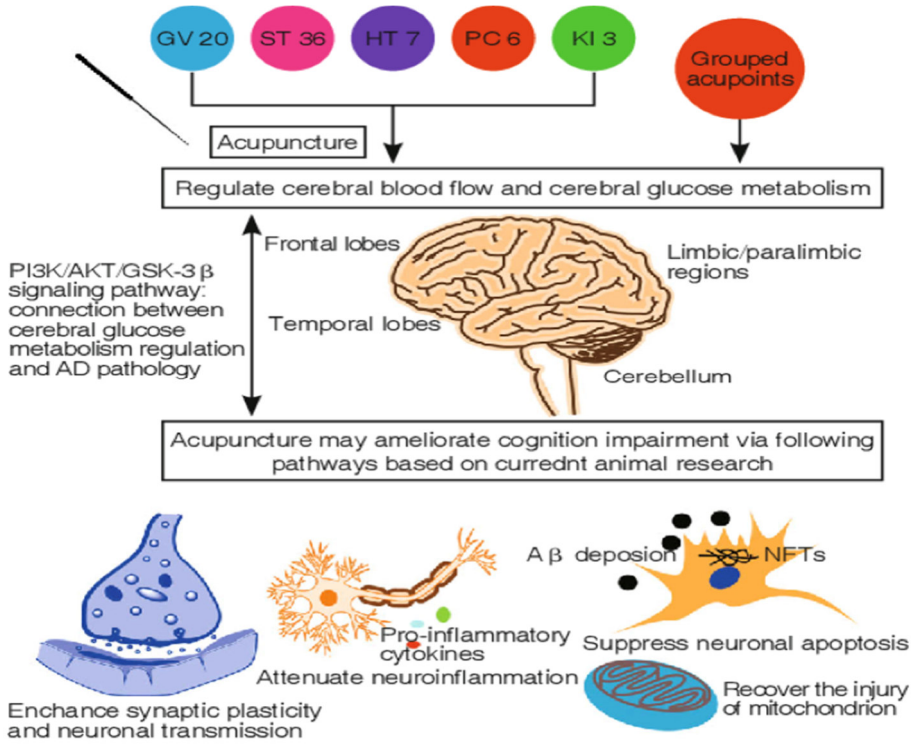

Figure 1. Acupuncture for Alzheimer's Disease.

A study looking at "proof of concept" to see if MBSR can reduce stress and change the hippocampal and default mode network. The outcome was that participants had increased functional connectivity between the posterior cingulate cortex, bilateral medial prefrontal cortex, and left hippocampus compared to controls. It also showed trends of less bilateral hippocampal volume atrophy [35]. Another study that supported the previous one used qualitative interview with participants who completed Mindfulness-Based Stress Reduction (MBSR), which showed that most adults with mild cognitive impairment (MCI) were able to learn mindfulness meditation and had improved MCI acceptance, self-efficacy, and social engagement [36].

A study protocol proposed a randomized controlled trial of residents with dementia in nursing homes in Germany. The intervention group listened to personally relevant music for 20 minutes every other day for 6 weeks. Nursing staff will assess their quality of life and problem behaviour at the 6-week baseline, pretest, post-test, and 6-week follow-up [37]. A group of 39 individuals with severe Alzheimer's disease were randomly and blindly assigned to two music intervention groups (passive and interactive) and a no-music control group. Emotional response and stress levels measured with the autonomic nerve index and the Face Scale were parameters for the evaluation of short-term effects. The Behavioral Pathology in Alzheimer's Disease Rating Scale was used to assess the long-term effects. Both passive and interactive music showed promising results, but interactive intervention had a more significant reduction of psychological symptoms of dementia (BPSD) compared to passive music intervention [38].

H. *Exercise*

Physical inactivity is a risk factor for developing Alzheimer's disease, and regular walking is linked to a twofold lower incidence of cognitive decline [39]. Studies have shown that exercise improves multiple types of memory, both long-term and short-term [40-47]. By lowering the risk of cardiovascular illness, boosting cerebral blood flow, expanding hippocampal capacity, and enhancing neurogenesis, this may also delay the start of AD [48].

A study had 39 patients randomized to an exercise group and a control group. Measurements by passive leg movement test and flow-mediated dilation were taken before and after the 6-month treatment. Blood samples were analyzed for vascular endothelial growth factor. Arterial blood flow and shear rate were measured during exercise and control groups during a typical treatment session. Results showed that exercise training improves peripheral vascular function in Alzheimer's disease [49]. In another study, 36 participants with amnestic mild cognitive impairment were randomized to two parallel groups under allocation concealment and assessor blinding. One group had choreography, while the other had physical therapy. Routines were done twice a week in 60 minute-sessions for 12 weeks. More significant cognitive benefits were achieved in choreography intervention than in physical therapy [50]. A study randomized parallel-group trial comparing the effects of centre-based to home-based exercise adherence among adults with a clinical diagnosis of mild cognitive impairment or mild dementia. The centre-based group will meet once a week as part of this study protocol to perform a small group exercise and an additional indecent activity. A series of activities that must be done on their own will be given to the home-based group. Each month, a phone call will be made to them to alter their workout regimens. The three sets of outcomes that this study will examine are physical function, cognition, mood, and quality of life [51]. It will also examine cost-effectiveness and the role of individual and environmental factors.

The use of yoga, computerized cognitive training, wellness instructors, and one-hour support groups will all be investigated in the proposed study. The trial will go for the whole 24 weeks. Functional connection and cerebral perfusion, as determined by MRI, are outcome measures, along with cognition, day-to-day activities, mood, anxiety, self-efficacy, caregiver load, and quality of life [52].

There is likely to be a continuously growing interest in the search for medications to mitigate, if not cure, Alzheimer's disease. Drug development efforts continue, but existing drugs are also being explored for their possible utilization in Alzheimer's disease [53]. As Alzheimer's disease is complex, other modes of management, such as enhancing the environment of patients with dementia, alongside the application of non-pharmacologic approaches, may prove to be beneficial.

Future Directions

In the coming years, more and more studies will be conducted on Alzheimer's disease. These will not be limited to research on new drug development only but also on existing molecules with potential for use in the disease. Advances in technology will pave the way for better drugs. However, patients will continue to seek alternative management due to their popularity and acceptability. Hence, research done on complementary and alternative medicine as non-pharmacologic management options should

continue. There will be more clinical data generated to support these alternatives and to prove their safety and even their cost-effectiveness. With ample data and reasonable evidence, these alternatives can be integrated into the clinical management of Alzheimer's disease.

Conclusion

Alzheimer's disease is a complex disease state requiring several management modalities to address its symptoms. Exercise or physical activity and methods to improve cognition, such as yoga and meditation, have published studies of their contribution to disease management. Acupuncture has also shown to be promising as part of management. More studies can be done on these alternatives in order to increase their significance and feasibility for inclusion into clinical practice.

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Authors contribution

All the authors have contributed equally.

Declaration of interest

The authors declare no conflict of interest.

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