

Managing Alzheimer's Disease through Alternative Therapy - Current Perspectives and Future Directions

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Abstract

The past four decades has witnessed considerable research progress in conventional medicine aiming to find a cure for Alzheimer's disease. Currently, even though there is no cure for the disease, a number of drugs can delay the deterioration of the symptoms and alter the disease progression. Alternative medicine, which has a long history in the treatment of ailments around the world, has been extensively used in patients who have dementia, with minimal side effects. Scientific inquiry into the effects of alternative therapy for managing Alzheimer's disease is way past its infancy and a familiarity for caregivers to advocate the use of alternative therapy as a conjunction intervention to standard care is warranted. In this review, the scientific evidence that supports the claim for adopting alternative therapy as part of the treatment regimen for Alzheimer's disease is discussed.

Keywords: Alzheimer's; Music Therapy; Acupuncture; Light; Aromatherapy

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia [1,2]. It is an age-related non-reversible disease that mostly affects elderly adults above the age of 65 [3]. Currently, it affects more than 5.4 million Americans [4]. AD targets complex neural networks that include structural and functional changes in neurons, neuroglia, and astrocytes [1,2,5,6]. AD is clinically characterized by progressive cognitive decline in addition to psychological disturbances, changes in some behavioral patterns and impairments in performing daily functions [7]. Multiple factors have been identified to play a role in the development of AD, but definitive causes that lead to this neurocognitive disorder are not well understood [8]. The multiple etiologies implicated in AD results in complex clinical phenotypes of the disease and this has further led to poor understanding of this multicellular dysfunction [9]. The lack of etiology specificity is attributed to a myriad of molecular factors that accounts for AD. The best recognized pathological features of individuals with AD are the presence of amyloid plaques and neurofibrillary tangles [5,6], leading to minimized functional efficiency of neurons and altered neuronal connectivity and communication progressively leading to neuronal death. The amyloid hypothesis postulates amyloid plaques responsible for the formation of neurofibrillary tangles composed of aggregated hyperphosphorylated tau [10]. As a multifactorial disorder, AD is commonly associated with a number of risk factors that includes obesity, diabetes, hypertension and inflammation [11-14]. Nonetheless, the modulation of the pathophysiology cannot fully explain the cognitive deficits and other associated symptoms observed. These behavioral/cognitive deficits have a severe impact on the quality of life of AD patients and are a major cause for institutionalization and mortality among the elderly population [4,7].

Sadly, as of now, there are no treatments available that cures AD [15]. A few drugs are effective in treating part of the wide array of disease symptoms; some that focus on the behavioral patterns and others that focus on aspects of cognitive impairment [16]. There is decreased cholinergic function in the brain of AD individuals. The standard treatment for AD involves therapeutic interventions with cholinesterase inhibitors or N-Methyl-D-Aspartate (NMDA) receptor antagonists which seem to improve cognitive function [16,17]. The blaring conundrum of using these drugs as the sole therapy is their association with multiple side effects and possibility of the drug not benefitting everyone [18]. Current treatments rationalize the need for fast symptomatic improvement of the disease rather than preventing, or blocking the cognitive decline seen in AD patients [17,18]. The strategies currently being pursued either target the pathology, genes or focus on the epidemiology [19]. However, in spite of all the research investigations, there is no cure for this debilitating disease. There is a dire need to venture into new therapeutic interventions and refocus our attention on existing complementary therapies that are necessary for the treatment of AD or even at least be able to temporarily relieve and improve some of the conditions without the possibility of having to be concerned about potential detrimental side effects.

The pathogenesis and etiology of AD are extremely convoluted. More effective therapeutic interventions and lifestyle modifications, ideally combinatorial, need to be pursued to effectively address AD and provide long term care with minimal side effects and maximal benefits to these individuals. Increased physical fitness in elderly people elevates cognitive performance and memory function. Randomized controlled trials in the elderly have provided evidence of even a modest enhancement of cognitive function in memory-impaired individuals who underwent a six month home based program of physical activity [20]. Positive associations between exercise interventions, brain structure and volume have been identified by numerous studies. Increased grey matter volume, associated with reduced cognitive decline [21] in the hippocampus, prefrontal cortex and the caudal nucleus has been reported [22-26]. A characteristic hallmark of old age is progressive degeneration of white matter which correlates with reduced cognitive function [27]. An increase in white matter integrity was observed after exercise intervention [28]. A healthy and planned diet has gained significant interest along with exercise interventions as modifiable protective factors. Incorporation of antioxidants like polyphenols in the diet can protect against the incidence of AD. Polyphenols from fruits and vegetables can confer neuro-protection through modulation of a number of cellular processes [29-31]. Similarly resveratrol, found in wine, is an effective antioxidant that inhibits signaling pathways offering protection against microglia dependent amyloid toxicity [32-33]. Intake of ketogenic diet also provides disease modifying benefits in AD [34-36]. An improvement of memory

after ingestion of medium chain triglycerides and essential fatty acids may be associated with decreased risk of developing AD [35,37-39]. Complementary and alternative therapies incorporate use of treatment methodologies outside the conventional medicine treatment and can be used to prevent the development, promote wellbeing and even cure the disease [40-42].

There are a number of alternative therapies that are currently being used in several neurocognitive diseases but so are the misconceptions associated with them [43,44]. It is important to note the presence of certain rampant unsubstantiated claims regarding the use of certain alternative therapies that make both patients and caregivers cautious about considering such approaches [44]. The objective of this current review is to provide some compelling evidence to certain important alternative approaches currently being used for AD, and how further scientific evaluation and studies are vital to further promote the use of these approaches as a prominent line of defense against AD. The enormous diversity of alternative therapy for AD is appreciated; however this review will focus on a few particular alternative therapies that show enormous promise in the treatment of several deficits associated with AD.

Music Therapy

Music therapy involves engagement of an individual in musical activities such as singing, listening to music or playing an instrument to accomplish individualized goals usually through the interaction with a licensed music therapist [45]. Numerous studies have documented the ability of dementia affected elderly, to respond better to music intervention compared to other non-pharmacological treatments [46,47]. Even with dementia, individuals have the ability to respond to music, even though other neurocognitive skills are deteriorating [48,49]. This emotion oriented treatment is often marginalized and misunderstood which makes it hard to integrate in a clinical setting. A non-pharmacological intervention, music therapy has been reported to reduce the level of agitation in elderly people who are cognitively impaired [50]. Even, the type of music intervention is important in altering the behavioral pattern in AD patients. Individualized music seems to be much more effective than classical relaxation music in minimizing agitation associated with AD [51]. A significant reduction in agitated behavior during meals in nursing home residents with severe cognitive impairment who were exposed to relaxing music [52] was achieved within weeks of music therapy [53]. Anxiety levels were lower in moderate to severe AD patients in a case control study of 38 patients with music interventions carried out by qualified music therapists [54]. Blood melatonin levels of AD patients who underwent 30 minutes of music intervention for 4 weeks were elevated suggesting the relaxed and calm mood following music therapy [55,56]. This effect persisted even after a 6 week follow up. Music therapy along with relaxation techniques reduces the levels of stress hormones, cortisol and β endorphin, thereby attenuating the HPA responses [57,58]. Heart rate, blood pressure, body temperature response changed due to reflexive brainstem responses initiated from exposure to music therapy [59]. Li, et al [60] demonstrated the benefit of music treatment on abstract thinking involving the use of concepts and generalizations, similar to a study which showed significant enhancement of spatial-temporal reasoning suggesting a possible functional plasticity that might be affected in AD patients as a result of music therapy [61]. There is also smaller number of negative behaviors and quantitatively elevated positive behaviors in people with dementia on days they received music therapy than on control days where no music interventions were performed [62]. Reminiscence plays an important role in music therapy since individuals often link the songs with their past memories [63]. Sharing of memories through

social interaction and developing healthy interactions between the individuals of the group and with the therapist provides an effective and feasible interventional module that could be incorporated in AD patients undergoing institutionalization or treatment [63]. Involvement in a reminiscence group helps in treating depressive symptoms associated with AD, where individuals tend to recollect personal histories better during these sessions along with better conversational skills [64]. A systematic review of the effectiveness of a number of mealtime interventions, including music therapy did suggest improvement of behavioral symptoms in elderly AD patients [65] although weak study designs limited making any strong conclusions. Ten studies from randomized clinical trials reviewed, suggested the methodological quality of the studies to be poor, and were unable to provide evidence that could either support or oppose the use of music therapy for people with dementia [66]. Different studies have utilized different measures of identifying treatment effectiveness and have provided conflicting results. Hence, better designed studies and multiple measures of treatment efficacy would provide clues to whether music therapy works in adjunct to pharmacological interventions in improving some of the behavioral symptoms seen in these patients [67]. More robust research methods with large controlled study groups and standardized treatment outcome measures are essential to establish and consider music therapy as evidence based non-pharmacological tool for the treatment of AD [68]. Use of music as an adjuvant to pharmacotherapy in geriatric care could in the long term, reduce the prescription of tranquilizers, hypnotics and help in the overall rehabilitation, mood elevation and improvement of physical and intellectual faculties. In any case, music therapy can be considered a low cost, simple alternative to conventional modes of therapeutics and has no known risk to the patient.

Acupuncture

This traditional Chinese medicine technique that involves the use of fine needles or the use of lasers has been practiced for ages in East Asia as an alternative treatment in memory impairment and for enhancing cognition in dementia and AD [69]. Revitalizing energy flow and pathways in the body to restore proper functioning is considered the foundation of acupuncture [69]. There is growing evidence on the effectiveness of using acupuncture as an effective primary and/or complementary therapy for AD. Recently, meta-analysis of randomized controlled trials identified acupuncture to be more effective than pharmacological treatments and additionally provides evidence to enhanced drug effects with simultaneous acupuncture therapy [70]. Decreasing neuronal death, inhibiting cell apoptosis and regulating the Glycogen Synthase kinase 3 (GSK3) and acetylcholinesterase levels are some of the suggested molecular mechanisms of acupuncture therapy in AD [71,72]. There is also increasing evidence in AD rat models, of the effect of acupuncture in reducing the amyloid beta protein through superoxide dismutase (SOD) elevation [73,74]. Improvement in the level of neurotrophic factors, inhibition of inflammatory molecules in the brain and upregulation of autophagy reactions are some additional mechanisms attributed to acupuncture therapy [75]. Governing Vessel 20 (GV20) is considered a very important acupuncture point in neurocognition. This acupoint belongs to the governor vessel and is located on the highest place on the head and is widely used in neurological and psychiatric diseases [76]. In rodents with vascular dementia, GV20 stimulation decreased the Region 1 of hippocampus proper (CA1) apoptotic neurons [77] by inhibiting tumor downstream components like tumor protein 53 (p53). B-cell lymphoma 2 (Bcl2) is an oncogene derived protein that blocks programmed cell death while Bcl2 associated X protein (Bax) is an apoptotic factor [78]. Acupuncture changes the pre-set ratio of Bcl2/Bax balance which is a transcriptional

target of p53 in vascular dementia [79], along with altering the expression levels and patterns of glutamate and NMDAR glutamate receptor respectively [80]. Through the coordinated performance of these molecules, acupuncture is suggested to promote memory and learning [81]. Electroacupuncture incorporating the use of a mild electric current passing through acupuncture needles have neuroprotective effects in the learning and memory centers of the brain that might prevent senile dementia [82]. Electroacupuncture might have greater benefits compared to manual acupuncture since this technique is more standardized and better measurable [83]. Moxibustion is a technique that is often combined with acupuncture [84]. Moxibustion incorporates heat therapy in the form of a burning, heated stick that is generally kept close to the body without touching the skin surface [84]. In AD rat models, moxibustion therapy with acupuncture shows significant reduction in the neuronal death rate and reduced neural edema with improved learning and memory [84]. Moxibustion, by itself, can hinder the progression and be used for the treatment of senile dementia, even though a combination of acupuncture and moxibustion can provide improved neuroprotective effect. This therapeutic combination increases the Mini Mental State Examination (MMSE) scores and improves the cognitive function of AD individuals with fewer occurrences of adverse events [76].

Aromatherapy

Aromatherapy in neurocognitive disorders involves the use of fragrant odors obtained from essential oils to promote mental health [85,86]. The mechanism of action of aromatherapy is still not fully understood, mostly due to inadequate research carried out to identify mechanistic pathways [87]. The mechanisms of the different aromatic oils are also varied between them [87]. Some of the anxiolytic effects of aromatic oils have been attributed to suppression of dopamine via enhanced serotonergic neuronal activity [87]. Lavender oil, for example is effective in controlling poor sleep patterns and increases sleep duration in dementia. It also reduces excessive motor activity and ameliorates agitation [88]. Multiple exposures of lavender oil reversed spatial memory deficits and had positive effects on memory formation, through regulation of the cholinergic system and anti-oxidant actions and reduced lipid peroxidation in the temporal lobe [89]. Lemon, rosemary and peppermint aromatherapy produced similar effects as well. Jimbo, et al [90] identified that effects of a cocktail of essential oils stimulates both the sympathetic and the parasympathetic nervous system of AD patients and improved the ability to form abstract ideas, conceptual understanding, cognitive function and movement. This sensory intervention showed significant reduction in aggressive behavior in elderly AD patients and promoted sleep to reduce anxiety in such patients. Olfactory dysfunction that includes deficits in identification, detection sensitivity and discrimination exists in AD [91,92], though the olfactory processing capabilities that are needed for achieving a beneficial effect is not known. It might be possible that the effect requires absorption into the circulatory system and not the olfactory nerve terminals. Aging and neurodegenerative diseases severely impairs olfactory functioning [93] and use of olfactory chemosensory stimulators that includes aromatherapy could serve beneficial effects in reversing or preventing the progression of Alzheimer type cognitive impairment [94]. Of the few randomized controlled trials in individuals with dementia, aromatherapy was suggested to be only as effective as placebo or anticholinesterase drug to treat agitation associated with dementia [95]. This is important as non-specific components of the aromatherapy which included touch and interaction with AD patients might be equally as important. Whatever the mechanism is, there is definitely a growing interest in studies involving use of aromatherapy for dementia in part due to the calming effect on agitation associated with AD.

Light Therapy

Normal aging is usually accompanied by a decline in sleep quality and a deterioration of the circadian rhythm [98,99]. Sleep fragmentation as a result of changes in the sleep cycle that impairs cognitive performance is a common finding in AD individuals [100]. Decreased exposure to bright light declines sleep quality while exposure to light resulted in a better consolidated sleep during night [101]. Light therapy is thus to be considered as a useful tool for betterment of sleep and circadian rhythm. The suprachiasmatic nucleus (SCN), known as the master clock, is the key region in the hypothalamus that regulates circadian rhythm. In mild to moderate cases of AD, bright light in the morning is effective in improving symptoms of agitation by delaying the duration of the agitation phase. Severe cases of AD did not benefit as much, as the SCN degenerates more with a subsequent deterioration of the sleep cycle rhythmic pattern [102]. "Sundowning" is a phenomenon seen in AD characterized by a cluster of behavioral patterns, including anxiety, confusion and some degree of aggression [103]. A lower degree of motor activity in the morning, higher level of nocturnal activity with a phase delay of body temperature is seen as part of sundowning [104]. This is seen during late day and at night, when the amount of lighting is low outside [104]. Light therapy to AD individuals who had sundowning and sleep disturbances improved ratings of sleep-wakefulness. Similarly, low level lighting used to stimulate daytime circadian cycle improved the behavior with concomitant reductions in depression scores and agitation scores, suggesting the applicability of light therapy in improving aspects of dementia [101]. Sleep disturbance and night time activity levels were minimized after a 2 hour treatment for a week [104]. Sundowning results in shorter sleep latency and increased sleep duration in patients with advanced dementia. Thus light therapy is an effective complementary therapy for improving the quality of sleep [105]. Indirect bright light increases the stability of rest-activity rhythm [106]. Most of the effects of light therapy on cognition are beneficial in the early stages of cognitive impairment and AD. Improved MMSE scores are seen in AD patients who have bright light therapy in the morning, even though no changes in the severity of dementia were seen. Non-pharmacological manipulation of an impaired SCN and thereby targeting the physiological circadian rhythm appears to be an effective approach to synchronize the rest-activity rhythm and enhance sleep, reduce anxiety and eventually elevate cognitive functioning in AD patients.

Conclusion

At present, there is no definitive treatment to prevent or cure AD. In fact, the complexity of the disease makes it very important to be able to use approaches that focus on multiple aspects of the disease with minimal side effects. Based on the clinical evidence published, alternative therapy components discussed in this review should be considered as an adjunct intervention as part of the treatment paradigm with current pharmacological options. There is a huge scope for alternative therapy research that might be beneficial in other aspects of AD as well. Expanding the research in this field will provide acceptance and incorporation of this practice into the mainstream medical practice and also promote investigations that can be useful in the development of newer drugs with a novel mechanism of action. Lack of standardized methods is a drawback in many aspects of alternative therapy research for AD, which could lead to inconsistencies in the studies; hence it is imperative to evaluate the effects of non-pharmacological interventions in larger controlled studies with standardized methods. Long term outcome reports on alternative therapy for cognitive impairment are currently insufficient limiting the ability to draw stronger and valid conclusions.

Olfactory screening tests might be valuable tools to predict the incidence of cognitive impairment [93,107], as with advancing age and in several neurodegenerative disease, olfactory loss and impairments in odor detection is observed [108], thereby supporting the need for aromatherapy as a prevention strategy for AD. Numerous studies have highlighted the potential for music therapy to improve the well-being of cognitively impaired individuals, suggesting the need for strengthening programs of multidisciplinary care of individuals with AD. Incorporating a longer duration with light therapy and well controlled experimental design with a large sample population is warranted to enable considering light therapy as an adjuvant to other treatment paradigms. Acupuncture shows tremendous potential and will need further exploration as a safe adjunct or alternative for the treatment of AD through improved methodological approaches and larger sample populations. Alternative therapies can mitigate the stress on the family and/or caregivers along with reducing the healthcare burden associated with institutionalizing, caring and treating AD. Experimentally rigorous studies incorporating non-drug interventions, that can influence the symptoms associated with AD, could hopefully improve the quality of life and promote the independence of the afflicted individuals. This would be crucial to advance and advocate the use of alternative therapy as a treatment approach.

Many AD patients and caregivers choose to try alternative therapies as part of a drug free lifestyle with the added desire of protecting them against further cognitive deterioration and improve the overall well-being. Non-pharmacological alternative therapy should eventually be part of standard care treatment for AD to reduce the neurocognitive deficits, associated behavioral and psychological impairments thereby improving the quality of life with minimum adverse effects and risks.

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