Alternative Approaches for the Treatment of Alzheimer's Disease

Margaret M Swanberg*

Department of Neurology, Uniformed Services University of the Health Sciences, Bethesda, Maryland

*Address for Correspondence

Margaret M Swanberg, Department of Neurology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, E-mail: Margaret. Swanberg@usuhs.edu

Abstract

Alzheimer's Disease is the most common dementia worldwide and the number of incident cases will continue to rise as the population ages. Despite the boom in drug development during the "Decade of the Brain", there has been a lull in newly approved medications to treat this devastating disease. Cholinesterase inhibitors and the N-methyl D-aspartate antagonist, memantine provide some benefit, however their effects are modest and they do no exhibit disease modifying activity. In part due to the lack of new agents, and the desire for better treatments, patients, families and healthcare providers are searching for alternative options. These potential options include herbal supplements, vitamin replacement, and medical foods. This review will focus on the putative action of some of these compounds, the existing data to support their use, and the cost of therapy.

Introduction

Alzheimer's disease (AD) is the most common dementia affecting the older population. According to the Alzheimer's Association 2016 Facts and Figures, 11% of the United States (US) population over age 65 has AD [1]. An estimated 5.4 million Americans have AD and incidence numbers suggest there will be approximately 172,000 new cases of AD in people between the ages of 75-84 [2]. AD, which causes impairment in memory, language, visuospatial function, and executive function poses significant challenges to the everyday life of both the patient and their caregiver(s). The economic burden of AD is estimated at $ 236 billion dollars [1].

There were significant advances made in the treatment of AD with the approval of four cholinesterase inhibitors (tacrine, donepezil, rivastigmine, and galantamine) in the 1990's and the N-methy-D-aspartate (NMDA) receptor antagonist memantine in 2003 [3-7]. Unfortunately, these medications only provide symptomatic relief and are not disease modifying therapies. Over the past decade research has predominantly focused on anti-β amyloid compounds with an additional handful of trials targeting tau-related pathophysiology. However these attempts at novel treatments resulted in a 99.6% failure rate [8].

In part due to the lack of success of recent clinical trials in AD, focus is turning toward other strategies to improve cognition in older age and possibly delay the onset of dementia. These strategies include use of nutraceuticals, vitamin supplements, and dietary modifications. This review will highlight some of the current research surrounding alternative approaches for the treatment of AD, with a focus on their putative mechanisms of action.

Herbal remedies

Herbal remedies have been used extensively in Asian countries, particularly China, as well as in Native American medical practices. These remedies are purported to heal and treat a variety of ailments affecting the body. Huperzine A, Gingko biloba, Ginseng, are increasingly popular as remedies for cognitive decline and will be discussed in more detail below.

Huperzine A

Huperzine A is a compound derived from the Chinese moss, *Huperziaserrata* and is used to treat fevers, swelling, and blood disorders. In the 1980's, Chinese scientists discovered its potent and reversible inhibition of cholinesterase activity [9]. Because of the role of acetylcholine in memory [10] and the loss of nucleus basalis of Meynart cholinergic neurons in AD [11]. Huperzine A is an attractive potential compound for the treatment of AD. When compared to prescription cholinesterase inhibitors, HuperzineA has a longer half-life and may have better tolerability [12]. In addition to its cholinesterase activity blockade, Huperzine A may reduce glutamate induced toxicity [13] and have anti-oxidant properties [14] as well.

A Cochrane Review on the use of Huperzine A in AD performed in 2008 suggested a possible beneficial effect, however only six randomized clinical trials, all performed in China, totaling 454 patients could be analyzed [15]. A second larger meta-analysis published in 2013 [16] examining 20 randomized clinical trials totaling 1823 patients found favorable results for Huperzine A on cognition when measured by Mini-Mental State Examination (MMSE) with the treatment group having a score that was 3.75 points higher at the 8 week mark and 2.79 points higher at 12 weeks (p<0.01, Confidence Intervals note reported). The Wechsler Memory Scale averaged 16.77 points higher after 8 weeks of treatment. However, two trials utilizing the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) found no difference compared to placebo (p=0.98). This same meta-analysis found that Activities of Daily Living (ADL) scales and Global Cognitive scales favored Huperzine A. Additionally, Huperzine A appeared to be well tolerated with adverse events similar to those of prescription cholinesterase inhibitors (nausea, vomiting, diarrhea, loss of appetite, bradycardia, etc). When compared to placebo in these studies, serious adverse events occurred in 8% in the placebo arms, 13% in the 200μg dose and 16% in the 400 μg dose (p=0.42 and p=0.20 respectively). A recently

published study examining the efficacy and tolerability of the four cholinesterase inhibitors plus memantine compared to Huperzine A plus memantine yielded positive results in favor of the Huperzine A plus memantine combination with respect to MMSE and ADL scores at 12 and 24 weeks, p<0.05. MMSE scores improved on average 4 points in the memantine plus cholinesterase patients, and scores improved 7 points in the Huperzine plus memantine group [17].

While Huperzine A may be an attractive target for the treatment of AD due to its potent cholinesterase blockade, larger well-designed clinical trials are still needed to assess efficacy. It should also be noted that studies of Huperzine A have generally not included data on quality of life or caregiver burden, therefore conclusions regarding these very important outcomes cannot be made. In general Huperzine A appears well tolerated and at an average cost of $ 20 for 100 capsules, it may be a considered for patients who cannot afford traditional prescription medications. Use of Huperzine A in combination with approved cholinesterase inhibitors should be discouraged.

Ginkgo biloba

Ginkgo biloba is a tree found throughout the world but is indigenous to Korea, Japan, and China. Extracts from the Ginkgo tree have been used for thousands of years to treat fever, asthma, circulatory disorders as well as cognitive dysfunction. In animal studies the standardized *Ginkgo* extract, EGb761, has been shown to improve mitochondrial function and neurotransmission, enhance microperfusion, and possibly modulate amyloid aggregation [18-22]. As a possible multi-target drug, EGb761 is one of the most widely used anti-dementia compounds and was included in the World Federation of Societies of Biologic Psychiatry Guidelines for the Biologic Treatment of Alzheimer's Disease and other dementias [23].

Numerous studies, including several randomized clinical trials have been published for EGb761 and the target dose appears to be 240 mg daily. An initial Cochrane Review published in 2009 found that EGb761 was safe and well tolerated, however there was a lack of consistent evidence regarding efficacy for the treatment of cognitive dysfunction in dementia. The trials evaluated in this review were generally small, of short duration, used differing doses of the extract, and did not use standardized dementia diagnostic criteria for all patients enrolled [24]. Additional trials have been published with varying results, but have also been marred by methodological flaws and/or small sample sizes. One of the few earlier published studies that had a large enough sample size failed to show a benefit of EGb761 on the prevention of dementia in older individuals [25]. Since the initial Cochrane Review, three additional meta-analyses have been published examining the efficacy and tolerability of Ginkgo [26-28]. These meta-analysis included many of the same studies and examined randomized clinical trials that were of at least 3 months duration, used standard dosing of EGb761, and employed accepted international criteria for the diagnosis of either Alzheimer's or Vascular dementia. Over 2000 patients were included in these meta-analyses and results from all 3 concluded that EGb761 showed a favorable benefit on cognitive measures (p=0.03), ADLs (p<0.001), and global impression scales (p=0.01). Additionally, EGB761 was found to be safe and well tolerated. The most recently published meta-analysis by Tan et al. further examined the effect of EGb761 versus placebo on dementia patients with neuropsychiatric symptoms and found an improvement

in Neuropsychiatric Inventory scores compared to baseline.

Based on pooled data from over 2000 patients enrolled in randomized clinical trials, EGb761, a standardized extract from the Gink*g*o tree appears to be a well-tolerated potential treatment for Alzheimer's disease and Vascular dementia. However, due to lack of large scale, high quality trials employing standardized diagnostic criteria for dementia the routine of Ginkgo biloba cannot be recommended.

Ginseng

Powders and extracts from *Panax ginseng* have been shown to have anti-oxidant and possibly anti-amyloid action as well [29,30]. In healthy adults without cognitive impairment, ginseng is believed to improve executive function, processing speed, and attention [31]. A Cochrane Review of 5 randomized trials in healthy adults found possible benefits on cognition, however the dosing of ginseng varied throughout the trials and only half of the trials included data on outcome measures [32]. Clinical trials assessing its effects in patients with Alzheimer's disease have had significant methodological flaws as well as very small sample sizes. Outcomes utilizing the MMSE, ADAS-Cog, and Clinical Dementia Rating scale (CDR) have been inconsistent [33]. Additional randomized controlled trials using accepted diagnostic criteria, standardized assessments, and larger patient populations are necessary prior to recommendation for routine use for the treatment of dementia.

Other Herbal Agents

Numerous other herbal compounds have shown promise in animal models of Alzheimer's disease. Many exhibit blockade of cholinesterase [34] and there is suggestion that some may have anti-inflammatory or anti-amyloid effects that could possibly have a disease modifying effect. Both garlic and curcumin have possible antioxidant effects and may prove beneficial, however human trials are lacking [35,36]. A readily available dietary supplement composed of royal jelly, Ginkgo biloba, and ginseng was studied in a randomized trial of patients meeting criteria for MCI [37]. This single study found a change in MMSE in favor of the treated group (+2.07 points compared to + 0.13). Obviously, larger studies need to be conducted before conclusions regarding this combination therapy can be drawn.

Vitamin supplements

The nutritional supplement industry generates close to $37 billion dollars a year, with an estimated $5.7 billion being spent on multivitamins. (http://www.marketwatch.com/story/most-us-adults-dont-need-dietary-supplements-2016-01-08). In general, a healthy diet is sufficient to provide adults with the vitamins and minerals that are necessary, however, data suggests that dietary intake of many vitamins including D and E are low in a significant percentage of the older population [38]. However, some data suggests that dietary insufficiencies, most notably Vitamin D and Vitamin E, may have an adverse effect on cognitive function in the elderly [39]. Recent studies examining the effects of these vitamin supplements will be reviewed below.

Vitamin E

Vitamin E is a lipid soluble anti-oxidant that is composed of α−,δ−

and, γ−tocopherols and tocotrienols. In rat models of AD, vitamin E supplementation appears to inhibit amyloid deposition through oxygen scavenger activity and may prevent brain degeneration. Numerous epidemiologic studies have suggested a positive effect of vitamin E levels on cognitive function in older adults [40-43]. It's believed that higher intake of all subtypes of tocopherolsare better for reducing the risk of developing AD compared to intake of only α-tocopherol.

In 1997 a landmark study looking at selegiline, alpha-tocopherol, or both for the treatment of Alzheimer's disease was published demonstrating positive effects of each therapy alone and in combination [44]. Since that time the efficacy and proper dosing of alpha-tocopherol in dementia and mild cognitive impairment patients has been debated with doses ranging from 400 IU up to 2000 IU. Despite being composed of α−, δ−, and γ−tocopherol, and data cited above suggesting benefit of all subtypes on cognition, most studies in dementia and MCI have used solely α-tocopherol which may account for some of the negative studies [45]. A Cochrane Review and found no evidence of a beneficial effect for Vitamin E treatment in dementia [46]. However, a large randomized controlled trial conducted at several Veteran's Administration Hospitals utilizing the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory demonstrated a positive effect on functional decline in mild/moderate AD patients (p=0.03) [47]. Petersen et al. examined over 700 patients to evaluate the rate of progression from MCI to AD. Patients were randomized to either placebo, vitamin E 2000iuor donepezil 10 mg and assessments were done over 36 months. Only donepezil appeared to slow progression over the first 12 months of the study, however not at the 36 month mark. Vitamin E had no effect on disease progression at any stage [48]. Vitamin E was also studied in patients over the age of 50 with Down's syndrome. Individuals were randomized to placebo or 2000iu of vitamin E with the primary outcome being change on the Brief Praxis Test (shown to be sensitive to decline in people with intellectual disabilities). After 36 months of study, there was no evidence that vitamin E slowed cognitive deterioration [49]. Preliminary studies by Mangialasche et al. and Morris et al. have supported the notion that a balanced intake of all tocopherols is more beneficial in reducing the risk of AD than pure α-tocopherol alone [50,51]. A 2015 study examined levels of various levels of brain tocopherols on Alzheimer's disease pathology and found that levels of γ-tocopherol were associated with lower amyloid plaques and neurofibrillary tangle load, suggesting that future studies should focus on γ-tocopherol [52].

The utility of vitamin E in preserving cognition, reducing risk of and treating AD has been debated over the past decade. However most of these studies focused on α-tocopherol, and there is growing evidence that total vitamin E supplementation (i.e. composed of all sub-types of tocopherol) is key. Prior to recommendations for widespread use of Vitamin E in patients with cognitive impairment or dementia, discussions regarding increased risk of hemorrhagic stroke should be had. A large analysis looking at over 118,000 patients found that vitamin E supplementation may reduce the risk of ischemic stroke, however there was a 22% increased risk of hemorrhagic infarct (relative risk of 1.22, p=0.045) [53]. For those patients who do wish to take vitamin E supplementation after careful consideration of stroke risk, isolated α-tocopherol should be discouraged due to its proven lack of efficacy.

Vitamin D

Vitamin D is a steroid vitamin first discovered in the 1800's. Ultraviolet rays from the sun are the main source of vitamin D with about 20% available through dietary intake. Two main forms, D2 (ergocalciferol) and D3 (cholecalciferol) are most commonly found in vitamin D supplements. Vitamin D deficiency/insufficiency has been linked to numerous human conditions including AD, cardiovascular disease, and multiple sclerosis [54,55]. With respect to the brain, vitamin D appears to play a role in learning and memory [56,57]. Vitamin D receptors are found throughout the brain with high concentrations in the temporal, orbitofrontal, and cingulate cortices, the thalamus, amygdala, and the nucleus accumbens [58]. Basic science research indicates that vitamin D has anti-inflammatory effects may reduce amyloid accumulation, and protect against glutamate toxicity [59,60].

Alzheimer's disease patients exhibit lower concentrations of vitamin D compared to matched controls, and numerous epidemiologic studies have demonstrated a relationship between hypovitaminosis D and overall cognitive function in non-demented older adults [61]. Non-randomized clinical trials suggested a positive effect on cognition (predominantly executive function and processing speed) following vitamin D supplementation, however supra-physiologic doses confer no additional benefit [57,62]. The Women's Health Initiative Memory Study (WHIMS) conducted a large randomized placebo controlled vitamin D plus calcium trial consisting in over 4000 women who were participants in the Women's Health Initiative study. Participants at entry did not have a diagnosis of dementia and the main outcome was progression to dementia or MCI using standardized criteria. Over a mean follow up of nearly 8 years, 4.8% of treated participants and 5.1% of placebo treated participants went on to develop either MCI or dementia. These results indicate there was no beneficial effect of vitamin D on progression to dementia or MCI in older women. Secondary outcomes included comparing a series of cognitive measures in the treatment and placebo arms. All tests failed to reach statistical significance (*p* values ranged from 0.14-0.98) [63].

Vitamin D supplementation may be warranted in older individuals at risk of dementia as it has numerous putative beneficial effects in the aging brain and in AD pathology. Although large scale trials assessing the utility of vitamin D supplementation in AD patients have not been conducted, it is feasible to obtain vitamin D levels in older patients and to supplement when indicated.

Medical foods

A medical food as defined by the United States Food and Drug Administration is a "food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation" [64]. Unlike supplements which are not regulated by the FDA, medical foods do require some evidence to prove their efficacy, however standards are not as rigorous as those required for traditional prescription medications. There are currently three

medical foods marketed in the US and/or Europe, that claim efficacy in the treatment of AD; Axona° (Accera, Inc, USA), Souvenaid° (Danone Research, France), and CerefolinNAC° (LA, USA). A fourth agent, Vayacog is only marketed for individuals with complaints of memory loss that do not yet meet criteria for dementia.

Axona

AD, there is decreased cerebral metabolism of glucose and reduced energy substrates as demonstrated by FDG PET. Axona, available by prescription, is a compound marketed by the US company Accera and was first released in 2009. It is a medium chain triglyceride composed of caprylic acid and glycerin. In the body, Axona is metabolized in the liver to the ketone β-hydroxybutyrate(BHB) and is believed to provide neurons with an alternate source of energy [65]. Because BHB enters mitochondria in the brain and enters a cascade that ultimately leads to ATP production, Axona is believed to slow cognitive decline through this mechanism.

phase II clinical trial composed of patients with mild to moderate AD, many of whom were on cholinesterase inhibitor therapy, demonstrated there was a statistically significant benefit on ADAS-Cog scores at day 45 of therapy (mean change from baseline of 1.9 points, p=0.02). The difference was maintained at day 90, however it was no longer statistically significant [66]. The adverse event rate was 23% in the treatment arm and 6% in the placebo arm. Most of the adverse events were secondary to gastrointestinal events (diarrhea, nausea, stomach upset, etc). The potential benefit of Axona may be greater in apolipoprotein E4 (APOE4) negative individuals with APOE4 (-) carriers demonstrating a mean difference compared to placebo of 5.73 points (p=0.002), however since testing for APOE status is not routinely done, the benefit of this medium chain triglyceride compound may have limited clinical utility [67]. Another open-label observational study of 22 Japanese patients who took Axona for a period of 90 days showed that it was well tolerated, however failed to demonstrate any improvement in cognitive function [68].

Axona presents a novel way to treat AD by targeting energy metabolism, with an estimated cost of $70-$80 per month. An insufficient number of randomized controlled trials are available to recommend routine use of Axona in the treatment of AD. Results of the few trials available do not support a sustained benefit beyond the 90 day mark. Due to ketone body formation, Axona should also be used with caution in patients with diabetes.

Souvenaid

One of the many pathologic hallmarks of AD is synaptic dysfunction as well as reduced synaptic density. This loss of synaptic function contributes to the cognitive dysfunction seen clinically. It is estimated that clinical symptoms manifest when synaptic density reaches 40% of that seen age-matched healthy individuals. This synaptic loss is also present in patients in the AD prodromal stage of MCI and may be more highly correlated with cognition function than presence of amyloid plaques or neurofibrillary tangles [69-72].

Souvenaid is a drink taken once daily, composed of a number of substances (uridine monophosphate, phospholipid, choline and omega-3 fatty acids, vitamins and antioxidants) that are believed to important for synaptic membranes. Preliminary safety and efficacy trials demonstrated a significant improvement on the Wechsler Memory Scale-revised (81% of patients showed either no change or improvement, compared to 68% in the placebo arm), however there was no difference on the ADAS-Cog [73]. The Souvenir II study was a multi-country study that looked at patients with AD who were not on traditional medical therapy with either a cholinesterase inhibitor or memantine. This trial used the Neuropsychological Test Battery (NTB) as the primary outcome measure due to suggestions that the ADAS-Cog may not be adequate to pick up change in patients with mild disease [74]. This study also used EEG as a measure of synaptic density. The NTB memory subscale showed a significant improvement at the 24-week point, however the composite score was not statistically significant. Functional disability measured with the Disability Assessment for Dementia found no difference at conclusion of the study. On the secondary outcome, measure of EEG change, investigators found there was less delta band slowing in the active treatment group compared to placebo suggesting there was a positive effect on synaptic function for Souvenaid. No differences in tolerability, dropout rate, or adverse events were seen between the active and control group. A 24-week open label extension study of Souvenir II examining safety and tolerability found at 48 weeks of Souvenaid treatment, the incidence of adverse events was similar to that noted in the randomized trial [75]. The NTB memory subscale was not a primary outcome, however analysis found a continued improvement in the initial active treatment group after 48 weeks of treatment. For those patients who were initially in the control arm of the randomized trial, there was a statistically significant increase in the NTB memory subscale during the 24-weeks of active treatment in the open label extension study (p=0.008). Results of a trial utilizing Souvenaid as part of the European LipidiDiet study [76] were presented at the 14th International Athens/Springfield Symposium on Advances in Alzheimer Therapy conference. This was a 24 month randomized double-blind controlled trial of mild AD patients who had a biomarker of AD pathology. The primary outcome, the NTB composite score failed to reach statistical significance. However there was a significant difference in hippocampal atrophy between the control and treatment group, "this brain structure had atrophied 39 percent more in the placebo than the treatment group" [77].

Souvenaid appears to have promising positive effects on biologic markers of AD, however clinical benefit seems to be marginal in patients with mild disease. Its effect or interaction with standard AD dementia treatment is also largely unknown. Additional randomized controlled studies, particularly in patients on standard medical therapy are warranted. Souvenaid is not currently available in the US.

CerefolinNAC

CerefolinNAC is a compound that presumably addresses the role of hyperhomocysteinemia and oxidative stress on cognitive function. Many studies have suggested that elevated total homocysteine levels are associated with brain volume loss, particularly gray matter volume in the medial temporal lobe [78], however supplementation with B vitamins generally results in little to no effect on cognitive outcome. CerefolinNAC composed of folic acid and B12 is recommended for treatment of AD patients that have significantly elevated levels of homocysteine. To date, there are no randomized placebo controlled

trials studying CerefolinNAC in AD. A case controlled study of CerefolinNAC in patients with dementia (not exclusively AD) used a variety of cognitive subtests as the outcome measure. Patients were allowed to be on stable doses of either cholinesterase inhibitor or memantine. Treatment with CerefolinNAC slowed cognitive decline with the most robust response being in those with a longer duration of treatment, milder disease, and higher baseline homocysteine levels [79]. In support of earlier studies suggesting a beneficial effect on brain volume, a 2016 study by Shankle et al. found slower atrophy rates in the cortex and hippocampus of AD patients who took CerefolinNAC [80].

The medical food, CerefolinNAC appears to slow brain atrophy rates in patients with elevated homocysteine levels, however randomized controlled trials measuring clinical and functional outcomes are non-existent. Studies determining if the beneficial effect on brain volume translates into a meaningful clinical outcome for patients are necessary. CerefolinNAC is available by prescription in the US and is not yet covered by most insurance plans. The monthly cost via the Brand Direct Health Pharmacy (which also provides Axona) is $58.

Conclusion

1990-2003 there was substantial progress made in the treatment of AD, with tacrine, donepezil, rivastigmine, galantamine, and memantine approved during this time period. However, recently, there has been a dirth of FDA approved medications. While substantial excitement exists for adacanumab as an anti-amyloid agent based on a Phase II study published in *Nature* [81], patients and caregivers are looking for alternative approaches to help slow down the progress of this devastating disease. It is prudent for healthcare providers to be aware of these various treatments options in order to have informed discussions regarding their utility and potential side effects. Although there is data regarding efficacy of the herbal supplements Huperzine A and Ginkgo biloba (as the standardized extract EGb761) as a potential option for the treatment of AD in patients who cannot afford traditional therapies or want additional options, the overall quality of this data is limited when compared to that available for more traditional therapies. Both herbals do appear to have favorable safety and tolerability profiles. Due to its cholinesterase inhibition, Huperzine A should not be used in concert with standard cholinesterase inhibitors. Vitamin D and E supplementation may also be considered for those patients that have either deficiency or insufficiency. When considering vitamin E supplementation, healthcare providers should have informed discussions regarding the increased risk of hemorrhagic stroke. If used, a complete supplement of vitamin E should be taken, as studies solely using α-tocopherol have been disappointing. Medical foods, available via prescription are potential options, however the agent with the most robust clinical evidence, Souvenaid is not available in the US. Due to ketone body formation, Axona should be used cautiously in patients with diabetes.

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