Utilization of vitamins, herbals, and over-the-counter products to delay progression of dementia

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ABSTRACT

Many consumers use alternative preparations such as herbals, vitamins, and over-the-counter products in an attempt to prevent or improve the outcome of dementia. Despite use by almost half of all patients, evidence supporting their utilization is either conflicting or lacking. Omega-3 fatty acids, vitamin B_6, vitamin B_{12}, vitamin C, and beta-carotene currently do not have clinical trials showing evidence impacting the progression or treatment of symptoms associated with dementia. In addition, conflicting data exist pertaining to the beneficial utilization of ginkgo biloba and nonsteroidal anti-inflammatory drugs associated with dementia treatment. While a link to the utility of folate associated with areas of improved cognitive functioning has been suggested, further studies are needed. Vitamin E may have some benefit in patients with Alzheimer's disease, however, may also have risks in patients with comorbid diseases such as cardiovascular disease or diabetes mellitus. With limited options still existing today in the treatment of dementia, the importance of further studies to quantify alternative therapies remains an important topic.

KEYWORDS

Vitamins, herbals, OTC dementia

UTILIZATION OF VITAMINS, HERBALS, AND OVER-THE-COUNTER PRODUCTS TO DELAY PROGRESSION OF DEMENTIA

Dementia is a broad term which encompasses several progressive neurodegenerative diseases. Currently, there are few drugs that have demonstrated efficacy in the treatment of symptoms. There is also a lack of disease-modifying agents available to impact progression of dementia. Many asymptomatic individuals concerned about the development of dementia, particularly when there is a family history, search for alternative treatments that may delay symptom evolution.

Frequently, these treatments involve herbal medications, vitamins, or over-the-counter medications, which may not have demonstrated efficacy, safety profiles, or established dose ranges. In an attempt to quantify alternative therapy usage, patients with dementia or mild cognitive impairment were questioned. Landin et al. found that 47% of patients with dementia utilized some form of alternative therapy, defined as drugs not approved for the treatment of dementia in Germany. As such, vitamins, over-the-counter medications, complimentary therapy, and herbal preparations were considered alternative therapy. Gingko preparations were measured, but were considered conventional medication due to approval in Germany. Of the patients utilizing alternative therapy, 72% of patients took vitamins, 23% took gingko biloba, and 14% took omega-3 fatty acids.[1] This article will review the use of several of these alternative medications.

ANTIOXIDANTS

One of the theories of the pathology of dementia is that there is an accumulation of free radicals and oxidative damage, which leads to neuronal deterioration. As an antioxidant, vitamin E (alpha-tocopherol) may scavenge free radicals, leading to decreased neuronal damage, thus modifying the progression of dementia. The Alzheimer's Disease Cooperative Study (ADCS) compared vitamin E (2000 IU per day), selegiline (10 mg per day), and the combination to placebo. Primary endpoints were progression to severe dementia, death, institutionalization, or a decline in activities of daily living (ADLs). Secondary endpoints involved several cognitive scales, such as the Mini-Mental State Examination (MMSE). After adjusting for higher MMSE scores in the placebo group, treatment groups showed an improvement in primary endpoints as compared to placebo. However, no difference was demonstrated between groups on secondary endpoints.[2] Based on the results of this study, the most recent American Academy of Neurology Practice Parameter for the management of dementia includes a recommendation on the use of vitamin E to slow the progression of pre-existing Alzheimer's disease (AD).[3]

Use of Vitamin E to slow the progression of AD may be limited in patients with underlying diabetes mellitus or cardiovascular disease. In a study of supplementation with Vitamin E, effects on the risk of cancer, cancer death, and cardiovascular disease were investigated. Patients with vascular disease or diabetes received either vitamin

E (400 IU per day) or placebo. After a mean treatment duration of seven years, participants in the vitamin E group had a statistically significant increased risk of heart failure.[4] Thus, the benefits of using vitamin E in patients with AD and either diabetes or cardiovascular disease may not outweigh the potential risks.

Studies of vitamin E in older adults who have not developed AD have differing results from the ADCS. Petersen and colleagues investigated agents to prevent progression to AD in patients with mild cognitive impairment (MCI). Patients received either vitamin E (2000 IU per day), donepezil (10 mg per day), or placebo. At the end of three years, no significant difference was found between groups in terms of disease progression.[5]

A similar lack of disease modification is found for the use of antioxidants in patients without baseline cognitive impairment. In the Age-Related Eye Disease Study (AREDS), participants received antioxidants (vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg); copper (2 mg) and zinc (80 mg); antioxidants, copper, and zinc; or placebo. Cognitive testing (Modified Mini-Mental State Examination, Animal Category, Letter Fluency, Digits Backwards, Logical Memory Part I and Logical Memory Part II from the Wechsler Memory Scale Revised, and Immediate Recall and Word List Mean from the Buschke Selective Reminding Test) was performed at baseline and at the seven-year follow-up. No differences among change in cognitive testing was found amongst the four groups.[6]

Patients in the Women's Antioxidant Cardiovascular Study (WACS) with coronary risk factors or cardiovascular disease were given antioxidants to determine if cognitive decline may be modified in patients with risk factors. Women received combinations of vitamin E (600 IU every other day), vitamin C (500 mg per day), beta-carotene (50 mg every other day), and placebo. Vitamin E and beta-carotene were not associated with a decrease in cognitive decline. Patients receiving vitamin C also did not show a change in cognitive decline over time, though they did show statistically significant improvement on the last cognitive testing (Telephone Interview of Cognitive Status, delayed recall of the TICS 10-word list, immediate and delayed recall of the East Boston Memory Test, category fluency test with animal names).[7]

Currently, data show that vitamin E may only be useful in patients with a diagnosis of AD, though potential risks exist for patients with underlying diabetes or cardiovascular disease. The ACDS study has some data supporting its use in treating AD, though the study may be limited by differences in baseline functioning between groups. The decision to supplement with vitamin E should be based on patient and caregiver preferences after a discussion of the potential risks and weak evidence supporting its use. Use of vitamin E or beta-carotene in patients with no or mild cognitive impairment is not supported at this time. Further research on the possible late effect of vitamin C needs to be conducted before it can be recommended in women with cardiovascular risk factors.

FOLATE AND B VITAMINS

Another theory behind the development of dementia is that hyperhomocysteinemia may be implicated in neurotoxic mechanisms. Homocysteine levels, which have been found to be elevated in AD, may be reduced by supplementation of folate, vitamin B_6, and vitamin B_{12}. In one study, patients with mild to moderate AD and normal homocysteine levels received either folate (5 mg per day), vitamin B_6 (25mg per day) and vitamin B_{12} (1mg per day) or placebo. Following eighteen months of treatment, patients who received vitamin supplementation had lower homocysteine levels, though no differences were found between groups on cognitive scales.[8] In another study conducted in hypertensive men, participants received vitamin B_{12} (500 mcg per day), vitamin B_6 (25 mg per day), and folic acid (2 mg per day) or placebo. Following two years of supplementation, there was no difference in the change of Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) between groups. There was also no significant difference at the eight-year follow-up of either risk of cognitive impairment or dementia.[9]

In contrast, patients with elevated homocysteine levels may benefit from supplementation. Durga et al. investigated the effect of supplementation with folic acid on atherosclerotic markers in patients with elevated homocysteine levels. A secondary outcome was effect on cognition. Participants received either folic acid (800 mcg per day) or placebo for three years. Patients were administered five cognitive function tests: word learning test, concept shifting test, Stroop color-word test, verbal fluency test, and letter digit substitution test. Changes in memory, information processing speed, and sensorimotor speed were statistically significantly improved in the folic acid group as compared to placebo. While this study may show that folic acid supplementation may improve some cognitive processing functions, it did not directly investigate effect on modifying development of dementia.[10]

Studies of folate and B vitamins are not as strong as there is differing methodology. Doses of supplements and length of supplementation between studies are not consistent. Length of supplementation in some of the studies may not have been adequate. Regardless, there is no robust evidence that shows that supplementation with folate, vitamin B_6, and vitamin B_{12} may be protective in the development of dementia.

ANTIINFLAMMATORY MEDICATIONS

Another theory behind the pathology of dementia is that there is an amyloid-induced inflammatory reaction. As such, anti-inflammatory drugs have been investigated as agents to delay the onset of AD or reduce the risk of development of the disease. Nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin use and the effect on risk of AD was investigated in the Baltimore Longitudinal Study of Aging. Among participants who reported use of NSAIDs, relative risk of AD decreased when use was two years or greater. No difference was found for aspirin users. [11] This suggests that NSAIDs, but not aspirin, may be protective against AD development. In contrast, Breitner et al. found that heavy NSAID use may be associated with an increased risk of dementia.[12] Pharmacy records were utilized to determine individuals who were defined as heavy NSAID users (>500 standard daily doses within two years). At the end of twelve years, there was an increased incidence of dementia in heavy NSAID users as compared to a group of individuals who were not heavy NSAID users.

The effect of low dose aspirin on the progression of AD was investigated in patients who had already been diagnosed with AD. Participants either received aspirin (75 mg per day) or were told to avoid aspirin. After three years, there was no difference between groups in either MMSE score or functional ability. In addition, the aspirin group had a statistically significant increase in serious bleeds.[13] This study illustrates that aspirin may have no benefit in modifying the progression of AD while placing patients at risk for significant bleeding events.

Use of NSAIDs to modify progression of disease in patients already diagnosed with AD was investigated utilizing naproxen and rofecoxib, which has since been withdrawn from the market. Participants received rofecoxib (25 mg per day), naproxen (220 mg twice daily) or placebo. Effect on ADAS-cog at one-year was examined and found to be not significantly different between groups.[14] Authors concluded that NSAIDs do not affect the decline of AD, though the previous study suggests that use longer than one year may be necessary.

At this time, conflicting data exist on the use of NSAIDs and aspirin for dementia. Confounding the use of these agents may be that the correct duration of use to show a significant effect has not been identified. There may also be a critical window for the timing of use of these medications to prevent development of dementia that has not been recognized. Furthermore, identification of recommended NSAIDs and dose range has yet to be elucidated. Currently, a recommendation on the use of NSAIDs or aspirin in the prevention or modification of dementia cannot be made.

OMEGA-3 FATTY ACIDS

Omega-3 fatty acids have become popular supplements for a variety of possible indications. Several theories support their use in dementia. As these supplements are reported to have a positive benefit on cardiovascular health, they may be beneficial in reducing risk of dementia through cardiovascular risk reduction. In addition, consumption of fatty acids is believed to be beneficial as these long-chain polyunsaturated fats have been found in membranes in the brain.

The effect of omega-3 fatty acids was studied in 204 patients with mild to moderate AD. Participants received docosahexaenoic acid (DHA) at a dose of 1.7 g per day and eicosapentaenoic acid (EPA) at a dose of 0.6 g per day or placebo. Following six months of therapy, no change in the rate of decline as measured on the ADAS-cog or the MMSE was found between groups.[15] Quinn et al. had similar results when comparing supplementation with DHA (2 g per day) and placebo in patients with AD. Rate of decline on the ADAS-cog after 18 months of therapy was similar between groups.[16] Thus, clinical trials do not currently support the use of omega-3 fatty acid supplementation as disease modifying agents in dementia.

GINGKO BILOBA

Gingko biloba originated as a traditional Chinese medication but use of its herbal preparation has increased throughout the world. It is postulated to play a role in AD as an antioxidant which may also increase blood supply and modulate neurotransmitter systems.[17] The effect of a gingko extract (GbE) was studied in patients with dementia over 52 weeks. Patients received either GbE (120 mg per day) or placebo. Statistically significant, as well as clinically significant to the caregiver, improvements in ADAS-cog and Geriatric Evaluation by Relative's Rating Instrument (GERRI) scores were found in the GbE group as compared to placebo. No differences between groups in terms of adverse effects were

identified[18] leading the authors to conclude that gingko biloba extract was a safe and effective therapy to improve cognition in dementia patients.

In contrast, Schneider et al. found that GbE did not have efficacy in the treatment of dementia. Participants received either GbE (120 mg per day or 240 mg per day) or placebo. After twenty-six weeks, there were no significant differences between groups on cognition as measured by the ADAS-cog, though this trial may have been too short in duration to show an effect.[19] Thus, conflicting data on the utility of gingko biloba in dementia exist in the literature.

Data on the use of gingko biloba in the prevention of dementia are also lacking. The effect of GbE was studied in elderly subjects with normal cognition or mild cognitive impairment. Participants received either GbE (120 mg twice daily) or placebo. At the end of the trial, there was no difference between groups in the number of participants who developed dementia.[20] Snitz et al. had similar results in a study in which participants also received either GbE (120 mg twice daily) or placebo. Changes in cognition as assessed by the Modified Mini-Mental Status Exam and ADAS-cog did not differ between groups.[21] Therefore, current evidence does not support that gingko biloba may play a role as a preventative therapy for dementia.

SUMMARY

Options for the treatment of dementia or the modification of the illness are currently limited. Many consumers turn to supplemental products such as herbals, vitamins, or over-the-counter medications in an attempt to slow or prevent decline. However, there is relatively little data to support such use. Vitamin E may be useful to slow the decline in patients with AD; however, concerns over its cardiovascular safety may limit its use. Studies have not shown utility of vitamin E in patients with no pre-existing cognitive impairment. Use of other antioxidants, such as vitamin C and beta-carotene, has not been shown to be of benefit in clinical trials. Data are also lacking on the use of omega-3 fatty acids in dementia.

Similarly, folate, vitamin B_6, and vitamin B_{12} have not shown benefits as protective medications to delay development of dementia. Further studies on the direct measure of dementia development are needed to determine the impact of folate in patients with baseline elevated homocysteine levels before its use as a supplement can be recommended in this population.

Conflicting data exist when examining effects of NSAIDs and gingko biloba on the progression of patients with dementia. While contradictory evidence also exists on the prevention of dementia with NSAID use, no support is seen on the use of gingko biloba in such patients. At this time, little recommendation can be made for the utility of alternative products in dementia. Though many patients use these products, the data supporting their use are lacking. Choice of supplement, appropriate duration of supplementation, critical timing of supplementation, and correct dose range for the supplement are questions that remain to be answered.

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