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Alzheimer's Disease

- Overview
- Definition
- Etiology
- Risk Factors
- Signs and Symptoms
- [Integrative Treatment Strategy](#)
- Prevention
- [Lifestyle](#)
- Drug Therapies
- [Nutrition and Dietary Supplements](#)
- [Botanical Medicine](#)
- [Acupuncture](#)
- [Massage and Physical Therapy](#)
- [Mind/Body Medicine](#)
- [Ayurvedic Medicine](#)
- Additional Considerations
- Complications/Sequelae
- Prognosis
- [References](#)

Integrative Treatment Strategy

No therapy—conventional, alternative, or complementary—can cure Alzheimer's disease. The goal of treatment, therefore, is to slow progression and lessen symptoms. It is possible that the earlier therapeutic measures are started, the more likely they are to have a benefit. To date, the approaches that appear to have the most promise for slowing progression and improving symptoms of Alzheimer's include:

- Medications such as donepezil—to inhibit cholinesterase
- *Ginkgo biloba* extract—contains flavonoids that act as antioxidants
- Behavioral (lifestyle) interventions—help control symptoms
- Vitamin E—acts as an antioxidant

Also of interest are herbal remedies that contain naturally occurring anti-cholinesterase activity, dietary intervention, and music therapy; but more research is needed in each of these areas before treatment recommendations can be made.

In determining an appropriate regimen, the needs of the caretaker must also be considered; 96% of caretakers report need/desire for help, but only 2% receive appropriate services.

Lifestyle

Preliminary studies suggest that incorporating the following strategies in caregiving may help improve behavior in patients with AD (Forbes 1998):

- A planned, supervised walking program with caregiver or other reliable companion; in one study, 30 minutes of walking 3 times per day improved communication; also, exercise may tire the patient enough to diminish wandering
- Bright-light therapy for control of insomnia as well as wandering; does not work in visually impaired
- Calming music (see [Mind/Body Medicine](#))
- Presence of a pet dog—studies show that this increased appropriate social behaviors
- Relaxation training and other exercises requiring focused attention (e.g., matching objects), coupled with reward with refreshments, may improve social interaction and the ability to perform the requested attention-dependent tasks in the short term.
- Use of the Safe Return program implemented by the Alzheimer's Association, in which the patient wears an

identification bracelet. In the event the patient goes missing, the caregiver can contact both the police and the Safe Return office, where information about the patient is stored and distributed nationwide.

Persons with Alzheimer's also have particular dietary concerns. They may need:

- Extra calories (in the case of increased physical activity)
 - Assistance with feeding (they must be fed or monitored to ensure that they do not forget to eat) and fluid intake (dehydration is not uncommon)
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Nutrition and Dietary Supplements

As discussed in Etiology, oxidative stress is thought to play a major role in AD. The value of supplemental antioxidants for treating AD has been raised and clinical trials are beginning to show promise, although results are not clear cut. Clinically, many physicians have been using antioxidants, particularly high dose vitamin E (Pitchumoni and Doraiswamy 1998).

Alpha-Tocopherol (vitamin E) and Ascorbic Acid (vitamin C)

Studies suggest that supplementation with vitamins E and C may benefit the patient with AD. The evidence supporting the use of vitamin E is stronger than that for vitamin C.

Vitamin E is fat-soluble and readily enters the brain. It inhibits lipid peroxidation, thereby maintaining the integrity of cell membranes (Tabet et al. 2000). A double-blind, placebo controlled, multi-center trial involving 341 patients followed for 2 years found that vitamin E 1000 IU bid increased survival time and improved clinical characteristics in patients with AD and moderate dementia (Sano et al. 1997).

In a large retrospective trial (the Honolulu-Asia Aging Study), vitamins E and C were associated with better cognitive performance in non-demented patients, and with significant reductions in vascular dementia and mixed/other dementias, but not specifically AD (Masaki et al. 2000). Interventional studies in people at risk for AD are needed to determine if and how these vitamins prevent or delay the onset of disease.

In a prospective study, 633 subjects over age 65 without signs of AD at baseline were followed for an average of 4.3 years; 91 developed AD in that time. None of the participants who took either vitamin E or vitamin C supplements at baseline later developed Alzheimer's disease. This finding was clinically significant compared to the number expected to develop AD (3.2 of the 23 vitamin C users and 3.9 of the 27 vitamin E users), suggesting a possible role for supplemental vitamin C and E for the prevention of AD (Morris et al. 1998).

S-adenosylmethionine (SAME)

SAME is involved in neurotransmitter metabolism (it is the major source of methyl groups in important methylation reactions in the nervous system) and also in vitamin B12 metabolism. Clinical studies suggest its usefulness in treating depression. A small study found significantly lower cerebral spinal fluid (CSF) levels of SAME in both AD and depressed patients compared to normal controls (Bottiglieri et al. 1990), and SAME and S-adenosylhomocysteine levels were lower in postmortem brain tissue of AD patients compared to brain tissue of both normal matched controls and subjects with Parkinson's disease. The latter finding suggests that depletion of these metabolites may be specifically connected to AD, rather than being the general result of a long-standing neurodegenerative disorder (Morrison et al. 1996).

CSF levels of SAME rose significantly after patients with AD took SAME (1200 mg/day in three divided doses) for 4 to 8 months, indicating that it does cross the blood-brain barrier (Bottiglieri et al. 1990). Clinically, improved cognition for some patients with AD taking SAME has been observed (Morrison et al. 1996). Further study of the relationship between SAME and AD is warranted (Bottiglieri et al. 1990; Morrison et al. 1996).

The following supplements have been evaluated and are sometimes used clinically for AD, but more research is required to determine if they may have a role in its management:

Carotenoids

Serum levels of beta-carotene and vitamin A were significantly lower in AD patients compared to controls while alpha-carotene levels were similar in the two groups (Jimenez-Jimenez et al. 1999). While intriguing, this association does not assume causality.

Folate and Cobalamin (Vitamin B12)

Folate has a role in reducing concentrations of homocysteine, and is important in the development of the central nervous system and metabolism of neurotransmitters. Low levels of folate may be associated with dementia and poor cognitive function (Snowdon et al. 2000). Higher levels of serum homocysteine and lower serum levels of both folate and vitamin B12 have, in fact, been found in patients

with AD compared to elderly volunteers without memory impairment (Clarke et al. 1998). These results however do not imply causality.

Omega-3 Fatty Acids

Polyunsaturated fatty acids (PUFAs) are involved in cellular functions that affect membrane fluidity and enzyme activity (Youdim et al 2000). Furthermore, docosahexaenoic acid (DHA), a 22-carbon PUFA, is the primary structural fatty acid in mammalian brain tissue. Age-related increases in oxidation are accompanied by lowered PUFA concentrations (Youdim et al 2000), and low levels of DHA have been associated with the structural and functional decline of brain tissue in general (Horrocks and Yeo 1999; Youdim et al 2000) and with AD specifically (Horrocks and Yeo 1999; Youdim et al 2000). Because the typical Western diet is high in n-6 and low in n-3 fatty acids, it has been suggested that a diet in which these acids are balanced (i.e. equivalent levels of n-6 and n-3 fatty acids or even a greater amount of n-3 compared to n-6) may delay onset or attenuate the effect of AD (Youdim et al 2000).

Coenzyme Q10 (ubiquinone)

Coenzyme Q10 is a mitochondrial component involved in the electron transport chain. It is an antioxidant, and may protect against glutamate-induced excitotoxicity (Ott and Owens 1998). It may have a potential therapeutic role in the treatment of Alzheimers.

Thiamine (vitamin B1)

Thiamine is necessary for thiamine-dependent enzyme activity in the brain and for cholinergic neurotransmission. In persons with AD, the activity of thiamine-dependent enzymes is decreased. Clinical studies using thiamine to treat cognitive decline, however, have conflicting results (Ott and Owens 1998). Larger, better-designed studies are needed to determine the value of thiamine for AD.

Phosphatidylserine (PS)

PS is a cell membrane component that maintains membrane integrity and fluidity as well as enhances acetylcholine and other neurotransmitter functions. Animal and cell culture studies suggest that PS can provide protection for the brain, and some clinical trials have suggested that PS may improve memory (Kidd 1999; Ott and Owens 1998). Double-blind trials suggest that PS may be beneficial in older persons with mild to moderate dementia and in middle-aged persons with age-related cognitive decline.

Flavonoids in Red Wine

Resveratrol, a flavonoid in red wine, has antioxidant, anti-inflammatory, anti-platelet, and estrogen-receptor agonist activities that may benefit AD patients (Ott and Owens 1998). However, there are no data to support a recommendation of wine for this population and risk of falls, alcohol-drug interactions, history of prior addictions, and sedative effects contributing to compromised cognition, preclude its recommendation. Red grape juice also has demonstrated antioxidant activity, although it contains less flavonoids than red wine.

Acetyl-L-carnitine

Acetyl-L-carnitine is similar in structure to acetylcholine and, therefore, has at least a theoretical role in treating AD (Ott and Owens 1998). Acetyl-L-carnitine is also a free radical scavenger and is involved in stabilization of the cell membrane and stimulation of nerve growth factor levels (Ott and Owens 1998; Pettegrew et al. 2000). Several controlled clinical trials have examined the role of acetyl-L-carnitine in treating AD, but results have been conflicting. Post hoc examination of the data from one trial suggested that acetyl-L-carnitine may be protective in the early stages of disease but may actually contribute to decline in later stages (Thal et al. 1996). Reported side effects include increased appetite, body odor, and rash. Recommendations for appropriate use of acetyl-L-carnitine for AD await more information.

Choline and Lecithin

AD patients appear to lack the enzyme necessary for converting choline into acetylcholine in the brain. Choline is a precursor for the neurotransmitter acetylcholine; lecithin is a major dietary source of choline. A meta-analysis of 12 randomized clinical trials found no clear benefit, however, for lecithin supplementation in treating either AD or dementia related to Parkinson's disease (Higgins and Flicker 2000).

Botanical Medicine

Ginkgo is widely used in European countries for treating dementia (Ernst and Pittler 1999). While many of the 40 double-blind clinical trials published to date have methodological flaws, the evidence for modest cognitive enhancing effects of *Ginkgo biloba* extract, particularly in the setting of AD, is highly suggestive. Research on other herbs is less convincing.

***Ginkgo biloba* (ginkgo)**

Ginkgo has been reported to have antioxidant activity, improve cerebral blood flow, inhibit platelet activation, affect neurotrophic and

receptor activities, and provide neuroprotection against ischemia (Mantle et al. 2000).

Clinical studies and meta-analyses appear strong enough to consider the value of ginkgo as a treatment for AD. Dosages in the range of 120 to 240 mg/day for periods of 1 month to 1 year have been associated with the following benefits, generally measured by the Alzheimer's Disease Assessment Scale (ADAS) or the Geriatric Evaluation by Relative's Rating Instrument (GERRI) (Ernst and Pittler 1999; Oken et al. 1998):

- Improved cognition
- Improvements in daily living
- Improved social behavior (Le Bars et al. 1997; Le Bars et al. 2000)
- Delay of AD symptoms
- Improved memory (Diamond et al. 2000)
- Reduced symptoms of depression (Diamond et al. 2000)

A literature comparison found that ginkgo's effectiveness was similar to that of the acetylcholinesterase inhibitors tacrine, donepezil, rivastigmine, and metrifonate in delaying the symptoms of dementia for AD patients (Wettstein 2000). Although side effects of ginkgo are typically minor, there have been reports of bleeding complications that include subdural hematomas; care should be taken especially if anticoagulants and, possibly, vitamin E are used (Mantle et al. 2000). Ginkgo exhibits MAOI effects, and therefore should not be used concomitantly with MAOIs (Diamond et al. 2000).

***Panax ginseng* (Asian ginseng) and *Panax quinquefolium* (American ginseng)**

The literature contains case reports that ginseng improves memory, learning, behavior, neuroendocrine function, intermediary metabolism, immune function, and the cardiovascular system. Although some tissue and animal studies support these claims, no clinical trials have been performed (Mantle et al. 2000).

***Nicotiana tobaccum* (tobacco)**

Nicotine, the principal alkaloid of the plant *N. tobaccum*, stimulates nicotinic receptors involved in cholinergic neurotransmission. Human studies indicate that nicotine may enhance memory in normal individuals and improve attention in AD patients. Animal studies have found memory improvement and inhibition of amyloid peptide formation in response to nicotine (Mantle et al. 2000). More research is necessary before determining the role, if any, for *N. tobaccum*; any potential for use of this substance will likely rely on development of nicotinic receptor analogues.

Acupuncture

Transcutaneous electrical nerve stimulation (TENS) for improvement in memory and function in Alzheimer's patients has produced some interesting findings in a few small, preliminary studies (Scherder et al. 2000; Scherder et al. 1995).

Massage and Physical Therapy

The inability to communicate normally with language increases anxiety and frustration in patients with AD. Using touch as a form of nonverbal communication (expressive physical touch, performed as a hand massage to each hand for 2.5 minutes with gentle, intermittent touching on the arm and shoulder) along with verbalization (i.e., calming speech) decreased pulse rate (a measure of anxiety) as well as dysfunctional behavior (assayed by E-BEHAVE-AD scores) over a 10-day period (Kim and Buschmann 1999).

Anecdotal evidence suggests that massage may offer several benefits to the patient with AD by providing:

- A prolonged period of contact with one individual
- Elicitation of the Relaxation Response
- A moderate form of exercise from manipulating muscles

Mind/Body Medicine

Music Therapy

Although music therapy has not been shown to slow or reverse dementia, it may improve quality of life for both patient and caregiver. No randomized controlled studies have evaluated the role of music therapy but clinical reports suggest it may improve social behavior and reduce wandering and restlessness (Koger and Brotons 2000).

One small study found that music therapy stimulated the neurohormonal and neurotransmitter systems. Significant increases were seen

in blood levels of melatonin, norepinephrine and epinephrine of 20 AD patients exposed to 4 weeks of live music for 30 to 40 minutes, 5 days a week. Increased levels of melatonin remained or continued to increase for 6 weeks after therapy ended. Observations made by therapists and nursing staff indicated positive behavioral changes that related to the music therapy (Kumar et al. 1999).

Support for the Caregiver

Although evidence is inconclusive, supporting caregivers by helping them cope with feeling of anger and frustration, providing an outlet for them to express their feelings, and educating them about AD not only improves their quality of life (Gwyther 1998; Thompson and Briggs 2000), but may delay decline in the patient. Certain support groups for caregivers follow a unique 12-step program designed specifically for this situation (Hagerty 1989).

Ayurvedic Medicine

Certain Ayurvedic herbs are traditionally used to treat cerebral deficits in elderly people:

- *Withania somnifera* (winter cherry)—has antioxidant and anti-inflammatory properties; in animal studies enhances stress tolerance (Archana and Namasivayan 1999; Dhuley 1998) and is a central nervous system depressant
 - *Herpestis monniere* (*Bacopa monniere*, or Brahmi)—in experimental models, *H. monniere* has been shown to improve motor efficiency and acquisition and retention of newly learned behavior (Bone 2000)
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