Nonconventional Treatments of Dementia/Mild Cognitive Impairment

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A review of nonconventional treatments for dementia and mild cognitive impairment, including dietary modification, Ginkgo Biloba, Huperzine-A, Phosphatidylserine, CDP-choline, Idebenone, and exercise.

If current population trends continue and treatments that arrest or reverse Alzheimer disease (AD) are not found, the number of patients with AD in the United States is projected to increase to more than 13 million by the year 2050. Numbers of persons afflicted with severe cognitive impairment caused by traumatic brain injury and stroke also continue to increase. Developing effective and cost-effective treatment approaches for AD and the other dementias is clearly an urgent priority. In addition to conventional pharmacologic treatments of dementia and milder forms of cognitive impairment, promising research findings are being reported for many nonconventional treatments. “Nonconventional” treatments are those biologic, somatic, mind-body, and energy-information approaches not currently accepted in Western biomedical psychiatry. This column provides a brief overview of the evidence for selected nonconventional approaches used to treat dementia and mild cognitive impairment in the United States and other Western countries. A review of more substantiated approaches in this issue will be followed in the next installment by highlights of approaches for which there is limited evidence at present.

**DIETARY MODIFICATION**

Epidemiologic studies, case control studies, and prospective trials suggest that persons who consume a high-fat, high-calorie diet are at significantly greater risk for AD than are persons who have moderate fat intake and restrict total calories. A meta-analysis of findings from 18 community-wide studies concluded that the risk of AD increased linearly at a rate of 0.3% with every 100-calorie increase in daily intake. However, a systematic review of 6 case control studies and 3 cohort studies that examined dietary preferences in dementia concluded that there is no compelling evidence for causal relationships between specific dietary factors and the risk of becoming demented. Consistent relationships between dietary protein, vitamins, and minerals and the risk of dementia were not identified. Evidence from epidemiologic studies suggests that regular intake of foods rich in omega-3 fatty acids may be inversely related to cognitive impairment or the rate of overall cognitive decline in nondemented elderly persons. However, findings to date are inconclusive. A large epidemiologic study concluded that consuming fish 2 to 3 times weekly significantly reduces the risk of cognitive decline in elderly populations. Cognitive impairment scores were analyzed for 2 groups of elderly men (aged 69 to 89) with different dietary preferences. High fish consumption was inversely correlated with cognitive impairment. Findings from a prospective cohort study suggest that persons who consume fish at least weekly have a 60% lower risk of AD than do persons who seldom eat fish. However, another study failed to show a correlation between fish consumption and the risk of AD. Moderate but not heavy consumption of wine (2 to 4 glasses per day) is also associated with a reduced risk of AD. In a large 2-year follow-up study, moderate alcohol consumption was found to be associated with a significant reduction in risk for both AD and vascular dementia.

**MEDICINAL HERBS AND SUPPLEMENTS**

**Ginkgo Biloba**

Standardized preparations of *Ginkgo biloba* are widely used in Europe to treat dementia and other neurodegenerative diseases. More recently, use of *G biloba* has become widespread in North America. Systematic reviews and early meta-analyses of double-blind controlled studies show that standardized preparations of *G biloba* in dosages between 120 and 600 mg/d taken for several weeks to 1 year result in consistent modest improvements. These improvements involve memory, general cognitive functioning, and activities of daily living in mild to moderate cases of both AD and multi-infarct dementia and are equivalent to improvements seen with donepezil (Aricept), a
conventional cholinesterase inhibitor. However, a more recent meta-analysis revealed inconsistent findings of 3 trials based on more rigorous research protocols and commented on research design problems in both recent and early impairtrials, including the absence of standardized ginkgo preparations and the use of different dementia rating scales across studies. Although most controlled studies fail to support the claim that ginkgo significantly improves memory in severely demented patients, the findings of one double-blind study suggest that the rate of overall cognitive decline is moderately slowed in this population.

A systematic review of 40 controlled and observational studies suggests that ginkgo improves cognitive symptoms associated with cerebral vascular insufficiency, including impaired concentration and memory loss.

To date, there is uneven evidence for beneficial effects of *G. biloba* in dementia. However, a review of research findings suggests that *G. biloba* extract should be regarded as a provisional approach for the prevention or treatment of mild cognitive impairment. A meta-analysis of 11 clinical trials of *G. biloba* extract in elderly persons who reported cognitive difficulties but did not meet full diagnostic criteria for dementia confirmed consistent cognitive-enhancing effects. However, more recent large studies on ginkgo in mild cognitive impairment have yielded negative findings. Long-term use of *G. biloba* extract in nonimpaired elderly persons may improve the efficiency and speed of information processing and delay onset of mild cognitive impairment. However, a recent, large controlled trial failed to confirm a consistent preventive effect.

Because of its strong anti-platelet aggregation factor profile, *G. biloba* extract increases the risk of bleeding and should not be used by patients taking aspirin, warfarin, heparin, or other medications that interfere with platelet activity and increase bleeding time. *G. biloba* preparations should be discontinued at least 2 weeks before surgery.

**Huperzine-A**

This alkaloid derivative of the herb *Huperzia serrata* is an important ingredient of many compound herbal formulas used in Chinese medicine to treat mild cognitive impairment that occurs with normal aging. Huperzine-A reversibly inhibits acetylcholinesterase and may also slow production of nitric oxide in the brain, possibly reducing age-related neurotoxicity. Controlled trials show consistent beneficial effects in both age-related memory loss and AD at dosages between 200 and 400 mg/d. Infrequent adverse effects include transient dizziness, nausea, and diarrhea.

**Phosphatidylserine**

This compound is one of the most important phospholipids in the brain and is an essential component of nerve cell membranes. The mechanism of action is believed to be enhanced fluidity of nerve cell membranes, indirectly resulting in increased brain levels of many important neurotransmitters. Brain-derived phosphatidylserine is probably more effective than the soy-derived product, possibly because of its higher content of docosahexaenoic acid, an omega-3 fatty acid, but recent concerns have been raised over the risk of slow viruses in infected bovine tissue. The findings of large, double-blind, placebo-controlled studies confirm improved global functioning and memory in AD and age-related cognitive decline at typical dosages of 300 mg/d. CDP-choline

**CDP-choline**

Cytidinediphosphocholine (CDPcholine) increases mitochondrial energy production and is used in many parts of the world to treat cognitive impairments that result from neurodegenerative diseases. CDP-choline, 500 to 1000 mg/d, improves overall energy metabolism in the brain, increases brain levels of dopamine and norepinephrine, and enhances short-term memory in patients with AD. Two Cochrane systematic reviews concluded that CDP-choline has consistent positive effects on the rate of recovery in post-stroke patients and in elderly persons who are cognitively impaired because of cerebrovascular disease. There is preliminary but promising evidence of a beneficial effect following traumatic brain injury. The findings of one small study suggest a possible effect of CDP-choline, 1000 mg/d, in the early stages of AD. Idebenone

*This is a substance that is related to ubiquinone (coenzyme Q10), and like that compound, it also increases intracellular energy production in mitochondria. Animal and human studies have shown that idebenone, 360 mg/d, may be more effective than tacrine (Cognex) and possibly other conventional treatments of cognitive impairment in mild to moderate cases of AD. However, in a large multicenter, doubleblind, placebo-controlled randomized trial, patients with probable early AD who received varying dosages of idebenone up to 300 mg tid did not experience slowing in the rate of cognitive decline compared with a control group.*

**SOMATIC AND MIND-BODY APPROACHES**

**Physical exercise**

Exercise increases levels of brain-derived neurotrophic factors, probably enhancing neural plasticity and new synapse formation. Regular exercise is associated with increases in the relative size of the frontotemporal and parietal lobes, which are important centers for learning, memory, and executive functioning. Long-term regular physical activity is associated with a reduced risk of all categories of dementia in elderly men and women.
More than 2000 physically nonimpaired men aged 71 to 93 years were monitored with routine neurologic assessments at 2-year intervals starting in 1991. At the end of the study period, men who walked less than a quarter of a mile daily had an almost 2-fold greater probability of having any category of dementia compared with men who walked at least 2 miles each day. Factors other than the level of physical activity were accounted for, including the possibility that limited activity could be a result of early but undiagnosed dementia.

Findings of the Nurses' Health Study, based on biannual mailed surveys over 10 years, showed that elderly women aged 70 to 81 years who engaged in regular vigorous physical activity were significantly less likely to have dementia than were women with more sedentary lifestyles. Although regular exercise is an important preventive strategy, it is probably not an effective intervention once dementia has begun. A randomized controlled trial showed that regular daily exercise in moderately demented individuals receiving in-home care reduces depressed mood but does not improve cognitive functioning.

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