Part 1

Nonconventional Treatments of Dementia/Mild Cognitive Impairment

f 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.2 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.3 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.⁴ 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

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.⁷ 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.⁸

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 Gbiloba 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.^{3,9-13}

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

trials, including the absence of standardized ginkgo preparations and the use of different dementia rating scales across studies.14 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. 15 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.16

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 impair-

ment. 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.¹⁷ However, more recent large studies on ginkgo in mild cognitive impairment have yielded negative findings.18 Long-term use of Gbiloba extract in nonimpaired elderly persons may improve the efficiency and speed of information processing and delay onset of mild cognitive impairment.19,20 However, a recent, large controlled trial failed to confirm a consistent preventive effect.21

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

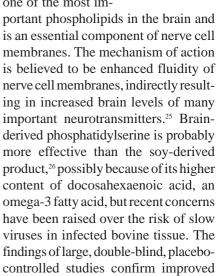
This alkaloid derivative of the herb *Huperzia serrata* is an important ingredient of many compound herbal formulas used in Chinese medicine to treat mild cognitive impairment that occurs with normal aging. Huperzine-A reversibly inhibits acetylcholinesterase and may also slow production of nitric oxide in the brain, possibly reducing agerelated neurotoxicity. ²² Controlled trials show consistent beneficial effects in both age-related memory loss and AD at dosages between 200 and 400 µg/d. ^{23,24}

by James Lake, MD

Infrequent adverse effects include transient dizziness, nausea, and diarrhea.

Phosphatidylserine

This compound is one of the most im-



global functioning and memory in AD

and age-related cognitive decline at typical dosages of 300 mg/d.²⁷⁻³¹

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,32 and enhances short-term memory in patients with AD.33 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.34,35 There is preliminary but promising evidence of a beneficial effect following traumatic brain injury.36 The findings of one small study suggest a possible effect of CDP-choline, 1000 mg/d, in the early stages of AD.37

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)³⁸ and possibly other conventional treatments of cognitive impair-

(Please see Nonconventional Treatments, page 42)



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Nonconventional Treatments

Continued from page 41

ment in mild to moderate cases of AD.³⁹ However, in a large multicenter, double-blind, 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.⁴⁰

SOMATIC AND MIND-BODY APPROACHES

Physical exercise

Exercise increases levels of brainderived neurotrophic factors, probably enhancing neural plasticity and new synapse formation.⁴¹ 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.⁴² 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 1991.⁴³ 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.8 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.44

Dr Lake is in private practice in Monterey, California and is an adjunct clinical instructor in the department of psychiatry and behavioral sciences at Stanford University. He cochairs the American Psychiatric Association Caucus on Complementary, Alternative, and Integrative Medicine (www.APACAM.org), and coauthor of Chinese Medical Psychiatry (Blue Poppy Press, 2001) and is author of the soon-to-be-published Textbook of Integrative Medical Health Care (Thieme).

References

- 1. Hebert LE, Scherr PA, Bienias JL, et al. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol.* 2003:60:1119-1122
- 2. Grant W. Dietary links to Alzheimer's disease. *Alzheimer's Dis Rev.* 1997;2:42-55.
- 3. Ernst E. Diet and dementia, is there a link? A systematic review. *Nutr Neurosci.* 1999;2:1-6.
- 4. Kalmijn S, Feskens EJ, Launer LJ, Kromhout D. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. *Am J Epidemiol*. 1997:145:33-41.
- 5. Morris MC, Evans DA, Bienias JL, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol*. 2003:60:940-946.
- 6. Engelhart M, Geerlings M, Ruitenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer's disease. *JAMA*. 2002;287:3223-3229.
- 7. Orgogozo JM, Dartigues JF, Lafont S, et al. Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area. *Rev Neurol (Paris)*. 1997;153:185-192.
- 8. Deng J, Zhou DH, Li J, et al. A 2-year follow-up study of alcohol consumption and risk of dementia. *Clin Neurol Neurosurg*. 2006;108:378-383. 9. Wong AH, Smith M, Boon HS. Herbal remedies
- 9. Wong AH, Smith M, Boon HS. Herbal remedies in psychiatric practice. *Arch Gen Psychiatry*. 1998:55:1033-1044.
- 10. Kanowski S, Herrmann WM, Stephan K, et al. Proof of efficacy of the *Ginkgo biloba* special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. *Pharmacopsychiatry*. 1996;29:47-56.
- 11. Oken BS, Storzbach DM, Kaye JA. The efficacy of *Ginkgo biloba* on cognitive function in Alzheimer disease. *Arch Neurol.* 1998;55:1409-1415.
- 12. Le Bars PL, Katz MM, Berman N, et al. A placebocontrolled, double-blind, randomized trial of on extract of *Ginkgo biloba* for dementia. North American EGb Study Group. *JAMA*. 1997;278:1327-1332.
- 13. Itil TM, Eralp E, Ahmed I, et al. The pharmacological effects of *Ginkgo biloba*, a plant extract, on the brain of dementia patients in comparison with tacrine. *Psychopharmacol Bull.* 1998;34:391-397.
- 14. Birks J, Grimley E. *Ginkgo biloba* for cognitive impairment and dementia (Cochrane Review). In: *The Cochrane Library*. Issue 2. Chichester, UK: John Wiley & Sons; 2004.
- 15. Le Bars PL, Velasco FM, Ferguson JM, et al. Influence of the severity of cognitive impairment on the effect of the *Ginkgo biloba* extract EGb 761 in Alzheimer's disease. *Neuropsychobiology*. 2002;45:19-26.
- 16. Kleijnen J, Knipschild P. *Ginkgo biloba. Lancet.* 1992;340:1136-1139.
- 17. Hopfenmuller W. Evidence for a therapeutic effect of *Ginkgo biloba* special extract. Meta-analysis of 11 clinical studies in patients with cerebrovascular insufficiency in old age [in German]. *Arzneimittelforschung*. 1994;44:1005-1013.

 18. van Dongen M, van Rossum E, Kessels A, et al.
- 18. van Dongen M, van Rossum E, Kessels A, et al. Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. *J Clin Epidemiol*. 2003;56:367-376.
- 19. Allain H, Raoul P, Lieury A, et al. Effect of two doses of ginkgo biloba extract (EGb 761) on the dual-coding test in elderly subjects. *Clin Ther.* 1993;15:549-558. 20. Semlitsch HV, Anderer P, Saletu B, et al. Cognitive psychophysiology in nootropic drug research: effects of *Ginkgo biloba* on event-related potentials (P300) in age-associated memory impairment. *Pharmacopsychiatry.* 1995;28:134-142.
- 21. Cheuvront SN, Carter R III. Ginkgo and memory. *JAMA*. 2003;289:547-548.
- 22. Zhao HW, Li XY. Ginkgolide A, B, and huperzine A inhibit nitric oxide-induced neurotoxicity. *Int Immunopharmacol.* 2002;2:1551-1556.
- 23. Wang Z, Ren Q, Shen Y. A double-blind controlled study of huperzine A and piracetam in patients with age-associated memory impairment and dementia. In: Kanba S, Richelson E, eds. *Herbal Medicines for Nonpsychiatric Diseases*. Tokyo: Seiwa Sholen Publishers; 1999:39-50.
- 24. Zucker M. Huperzine-A: the newest brain nutrient. *Let's Live*. 1999:47-48.
- 25. Pepeu G, Pepeu IM, Amaducci L. A review of phosphatidylserine pharmacological and clinical effects. Is phosphatidylserine a drug for the ageing brain? *Pharmacol Res.* 1996;33:73-80.
- 26. Hibbeln JR, Salem N Jr. Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. *Am J Clin Nutr.* 1995;62:1-9.
- 27. Cenacchi T, Bertoldin T, Farina C, et al. Cognitive decline in the elderly: a double-blind placebo-

controlled multicenter study on efficacy of phosphatidylserine administration. *Aging (Milano)*. 1993:5:123-133.

- 28. Crook TH, Tinklenberg J, Yesavage J, et al. Effects of phosphatidylserine in age-associated memory impairment. *Neurology.* 1991;41:644-649.
- 29. Villardita C, Grioli S, Salmeri G, et al. Multicentre clinical trial of brain phosphatidylserine in elderly patients with intellectual deterioration. *Clin Trials J*. 1987:24:84-93
- 30. Palmieri G, Palmieri R, Inzoli M, et al. Doubleblind controlled trial of phosphatidylserine in patients with senile mental deterioration. *Clin Trials J*. 1987:24:73-83.
- 31. Amaducci L. Phosphatidylserine in the treatment of Alzheimer's disease: results of a multicenter study. *Psychopharmacol Bull.* 1988:24;130-134.
- 32. Secades JJ, Frontera G. CDP-choline: pharmacological and clinical review. *Methods Find Exp Clin Pharmacol.* 1995;17(suppl B):1-54.
- 33. Alvarez XA, Laredo M, Corzo D, et al. Citicoline improves memory performance in elderly subjects. *Methods Find Exp Clin Pharmacol.* 1997;19:201-210. 34. Mitka M. News about neuroprotectants for the treatment of stroke. *JAMA*. 2002;287:1253-1254. 35. Fioravanti M, Yanagi M. Cytidinediphospho-
- 35. Fioravanti M, Yanagi M. Cytidinediphosphocholine (CDP Choline) for cognitive and behavioral disturbances associated with chronic cerebral disorders in the elderly (Cochrane Review). In: *The Cochrane Library.* Issue 2. Chichester, UK: John Wiley
- 36. Spiers PA, Hochanadel G. Citicoline for traumatic brain injury: report of two cases, including my own.

- J Int Neuropsychol Soc. 1999;5:260-264.
- 37. Alvarez XA, Mouzo R, Pichel V, et al. Double-blind placebo-controlled study with citicoline in APOE genotyped Alzheimer's disease patients. Effects on cognitive performance, brain bioelectrical activity and cerebral perfusion. *Methods Find Exp Clin Pharmacol.* 1999;21:633-644.
- 38. Gutzmann H, Kuhl KP, Hadler D, Rapp MA. Safety and efficacy of idebenone versus tacrine in patients with Alzheimer's disease: results of a randomized, double-blind, parallel-group multicenter study. *Pharmacopsychiatry.* 2002;35:12-18.
- 39. Gutzmann H, Hadler D. Sustained efficacy and safety of idebenone in the treatment of Alzheimer's disease: update on a 2-year double-blind multicentre study. *J Neural Transm Suppl.* 1998;54:301-310. 40. Thal LJ, Grundman M, Berg J, et al. Idebenone treatment fails to slow cognitive decline in Alzheimer's disease. *Neurology.* 2003;61:1498-1502.
- 41. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci.* 2002;25:295-301.
- 42. Haier RJ. Cerebral glucose metabolism and intelligence. In: Vernon PA, ed. *Biological Approaches to the Study of Human Intelligence.* Norwood, NJ: Ablex Publishing; 1993:318-332.
- 43. Abbott RD, White LR, Ross GW, et al. Walking and dementia in physically capable elderly men. *JAMA*. 2004:292:1447-1453
- 44. Teri L, Gibbons LE, McCurry SM, et al. Exercise plus behavioral management in patients with Alzheimer's disease: a randomized controlled trial. *JAMA*. 2003;290:2015-2022. □