

Nonconventional Treatments of Cognitive Impairment

by James Lake, MD

In the first part of this article (*Psychiatric Times*, June 2006, page 41), I pointed out that the numbers of patients with Alzheimer disease (AD), as well as those with severe cognitive impairment caused by traumatic brain injury and stroke, are continuing to increase. I noted that in addition to conventional pharmacologic treatments, promising research findings are being reported for many nonconventional treatments. In that column, I reviewed the more substantiated nonconventional approaches. This month, I look at some approaches for which the evidence is more limited.

HERBS AND SUPPLEMENTS

Kami-untan-to

This compound herbal formula consists of 13 different herbs. It is used in Japanese traditional healing (Kampo) to treat cognitive impairment and frank dementia, as well as other psychiatric symptoms. Animal studies suggest that kami-untan-to (KUT) increases brain levels of both nerve growth factor and choline acetyltransferase, the enzyme that makes acetylcholine.¹²

In a 12-month open trial, 20 patients with moderate dementia and AD who received KUT alone and 7 who received a combined regimen of vitamin E, estrogen, and a nonsteroidal anti-inflammatory drug deteriorated at a significantly slower rate than 32 control patients with moderate dementia who received no treatment.³ The beneficial effects of KUT were most notable 3 months into the study.

Golden root

Golden root (*Rhodiola rosea*) was the object of intensive research in the former Soviet Union because of its use as a performance enhancer in athletes, soldiers, and cosmonauts. Psychiatric benefits are probably related to increased dopamine, serotonin, and norepinephrine levels in the brain⁴ and include improved memory, increased mental stamina, and a general calming effect. Results from open studies suggest that golden root, 500 mg/d, improves overall mental performance and stamina in healthy persons⁵ and may accelerate return to normal cognitive functioning following traumatic brain injury. No studies on the use of golden root in dementia have been done.

Acetyl-L-carnitine

This substance occurs naturally in the brain and liver. Its mechanism of action may involve stabilization of nerve cell membranes, stimulation of acetylcholine synthesis, and increased efficiency of mitochondrial energy produc-

tion. Acetyl-L-carnitine (ALC) is widely used to treat and self-treat cognitive impairments related

to dementia or other neurodegenerative diseases; however, findings from human clinical trials are inconsistent.⁶

Three small double-blind placebo-controlled studies show that ALC, 1500 to 3000 mg/d, improves overall performance on tests of reaction time, memory, and cognitive performance in patients with dementia and may slow the overall rate of progression of cognitive impairment.⁷⁻⁹ A Cochrane systematic review of 11 double-blind placebo-controlled studies of ALC in dementia confirmed significant positive effects at weeks 12 and 24, but these were not sustained at 1 year with continued treatment.¹⁰ ALC is well tolerated, and there are few reports of adverse effects.

B vitamins

Certain B vitamins are essential enzyme cofactors in the synthesis of neurotransmitters. A diet low in folic acid and B₁₂ leads to elevated blood levels of homocysteine and decreased synthesis of S-adenosyl methionine (SAME), resulting in reduced synthesis of several neurotransmitters critical for normal cognitive functioning. Dietary deficiencies of folate and B₁₂ eventually manifest as moderate to severe cognitive impairment.

In a double-blind placebo-controlled study of 5-methyltetrahydrofolate (a form of folate), 50 mg/d, patients with dementia who were depressed experienced significant improvements in both mood and memory after 4 weeks of therapy.¹¹ However, the relationship between cognitive functioning and folate remains unclear. A Cochrane systematic review of 4 controlled studies concluded that there is insufficient evidence to support the use of folic acid with or without B₁₂ as a treatment for dementia or other forms of severe cognitive impairment.¹² Supplementation

with large dosages of thiamine (3 to 8 g/d) may result in mild improvement in cognitive impairment in patients with AD.¹³

A few small open studies have evaluated the efficacy of B₁₂ as a cognition-enhancing agent in elderly patients who were moderately impaired and nondemented. Eighteen elderly patients with low serum B₁₂ levels were given injections of B₁₂ following a strict protocol: daily 1-mg injections for the first week, followed by weekly 1-mg injections for 1 month, then

monthly 1-mg injections for 6 months. All patients in the study improved, and those who had been cognitively impaired for less than 1 year experienced the most significant gains.¹⁴

Part 2

Vitamins C and E

These important antioxidants function as free-radical scavengers throughout the body and brain, possibly slowing progression of AD and other neurodegenerative diseases. The findings of a large epidemiologic study show a correlation between intake of vitamin C and E in the form of supplements and reduced risk of AD.¹⁵ This effect was greatest for vitamin E.

Anecdotal reports suggest that supplementation with vitamins C and E improves cognitive functioning in patients with AD, but few controlled studies have been done, and the findings of observational studies are inconclusive or negative.^{16,17} A Cochrane review identified only one study of vitamin E in dementia that met rigorous inclusion criteria. That study failed to provide clear evidence of improved global or cognitive functioning or reduced behavioral disturbances in persons with moderate dementia.¹⁸

Combining vitamins E and C may reduce the prevalence and incidence of AD. A prospective 5-year study followed 4740 adults aged 65 and older.¹⁹ At the end of the study, there were 104 new cases of AD. A strong inverse correlation was found between the incidence and prevalence of AD and combined use of vitamin C (at least 500 mg/d) and vitamin E (at least 400 IU/d). However, there was no association between the use of vitamin C alone, vitamin E alone, or a multivitamin alone and the incidence or prevalence of AD. Large doses of vitamin E are associated with an increased risk of bleeding. Persons who are at increased risk of stroke should consult their physi-

cian before starting a high-dose vitamin E regimen.

DHEA

Dehydroepiandrosterone (DHEA) is a precursor of testosterone and other hormones. DHEA binds to both γ -aminobutyric acid receptors and N-methyl-D-aspartate receptors, but it is not clear whether these receptor affinities are related to its putative cognition-enhancing role.²⁰ A Cochrane systematic review and meta-analysis found no support for the use of DHEA as a cognitive enhancer in healthy older persons.²¹ However, there is limited evidence that DHEA 200 mg/d may improve symptoms of cognitive impairment in patients with multi-infarct dementia.²² To date, no controlled trials have been done on DHEA in AD.

Testosterone

Limited evidence suggests that testosterone replacement therapy may improve global functioning in persons with mild AD. In a 6-month, randomized, double-blind, placebo-controlled study, 47 men aged 50 and older were randomized to receive testosterone 75 mg/d or placebo together with their usual medications. The study included healthy controls and patients with mild dementia. Global quality of life improved in both the mildly demented group and the healthy controls. Patients with mild dementia who received testosterone experienced less decline in overall functioning and visual-spatial abilities. Men who have benign prostatic hypertrophy or prostate cancer should avoid the use of testosterone.

OTHER APPROACHES

Essential oils

Essential oils can be used as aromatherapy or applied directly to the skin during massage. Recent findings suggest that certain essential oils have beneficial calming effects on agitation in patients with dementia. A Cochrane systematic review found only 1 study that met inclusion criteria, and although the outcome of that study was positive, the reviewers concluded that methodologic problems limited the significance of its findings.²³ In other studies, the essential oils of lemon balm and lavender reduced agitated behavior in

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persons with dementia when topically applied directly to the face and arms.^{24,25}

Possible adverse effects include skin allergies, phototoxic reactions, and potentiation of sedative-hypnotic medications when used with lavender or other oils known to have sedating effects. Pregnant women should exercise

caution when considering aromatherapy because of possible effects on the fetus and uterus caused by systemic absorption of certain essential oils.

Electric current

The application of weak electric current to the head or neck may temporarily improve memory, behavior, and activities of daily living in patients with dementia.^{26,27} A Cochrane meta-analysis of 3 studies of transcranial electri-

cal nerve stimulation devices used to treat dementia found evidence of significant but transient improvements in word recall, face recognition, and motivation immediately following treatment.²⁸ Most research findings show that improvements are not sustained 6 weeks or more after treatment is terminated.

Music

Music is used in many healing traditions to calm the mind and reduce

agitated behavior. Findings of a meta-analysis evaluating studies of music therapy in persons with dementia show that various approaches—singing, dance, listening to music, and musical games—are associated with improvements in cognitive and behavioral functioning in persons with severe dementia, including reduced agitation, reduced wandering, enhanced social interaction, improved mood, reduced irritability and anxiety, increased cooperative behavior, and improved performance on standardized scales including the Mini-Mental State Examination.²⁹

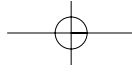
Regular music therapy was shown to reduce irritability and to improve expressive language in persons with dementia.³⁰ Listening to binaural sounds in the beta frequency range (16 to 24 Hz) using headphones may enhance performance on tests of attention and short-term and immediate recall in healthy volunteers.³¹

Touch may have beneficial effects in patients with dementia.

Healing touch

Open studies, case reports, and one double-blind trial suggest that Healing Touch (HT) and Therapeutic Touch (TT) have beneficial effects on agitation in patients with dementia. In one small open study, measures of agitation were significantly improved in 14 residential patients with dementia who received 3 HT treatments weekly over a 4-week period.³² Diminished need for psychotropic medications was observed in 3 patients during the active treatment phase, and 2 residents required dose increases in the first 2 weeks after HT treatments were stopped.

In another small, sham-controlled study, 3 weekly 10- to 20-minute HT treatments were administered to patients with AD over a 5-week period. Patients who received regular HT treatments were found to have consistent reductions in disruptive behaviors and globally improved emotional and cognitive functioning, including enhanced socialization, a more regular sleep schedule, improved compliance with nursing home routines, greater emotional stability, and improved communication with staff. In a double-blind study (N = 57) that included mock TT in the control arm, agitated patients with dementia who received 2 brief TT treatments daily for 3 days exhibited significantly fewer behavioral symptoms of dementia, including



reduced restlessness and fewer disruptive vocalizations, than patients who received mock TT.³³

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References

1. Yabe T, Torizuka K, Yamada H. Kami-untan-to (KUT) improves cholinergic deficits in aged rats. *Phyto-medicine*. 1996;2:253-258.
2. Yabe T, Yamada H. Kami-untan-to enhances choline acetyl-transferase and nerve growth factor mRNA levels in brain cultured cells. *Phyto-medicine*. 1996/1997;3:361-367.
3. Arai H, Suzuki T, Sasaki H, et al. A new interventional strategy for Alzheimer's disease by Japanese herbal medicine [in Japanese]. *Nippon Ronen Igakkai Zasshi*. 2000;37:212-215.
4. Petkov VD, Stancheva SL, Tocuschieva L, Petkov VV. Changes in brain biogenic monoamines induced by the nootropic drugs adafenoxate and meclofenoxate and by citicholine (experiments on rats). *Gen Pharmacol*. 1990;21:71-75.
5. Spasov AA, Wikman GK, Mandrikov VB, et al. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of *Rhodiola rosea* SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. *Phyto-medicine*. 2000;7:85-89.
6. Pettegrew JW, Levine J, McClure RJ. Acetyl-L-carnitine physical-chemical, metabolic and therapeutic properties: relevance for its mode of action in Alzheimer's disease and geriatric depression. *Mol Psychiatry*. 2000;5:616-632.
7. Arrigo A, Casale R, Buonocore M, Ciano C. Effects of acetyl-L-carnitine on reaction times in patients with cerebrovascular insufficiency. *Int J Clin Pharmacol Res*. 1990;10:133-137.
8. Thal LJ, Carta A, Clarke WR, et al. A one-year multi-center placebo-controlled study of acetyl-L-carnitine in patients with Alzheimer's disease. *Neurology*. 1996;47:705-711.
9. Calvani M, Carta A, Caruso G, et al. Action of acetyl-L-carnitine in neurodegeneration and Alzheimer's disease. *Ann N Y Acad Sci*. 1992;663:483-486.
10. Hudson S, Tabet N. Acetyl-L-carnitine for dementia (Cochrane Review). In: *The Cochrane Library*, Issue 2. Chichester, UK: John Wiley & Sons, Ltd; 2004.
11. Passeri M, Cucinotta D, Abate G, et al. Oral 5'-methyltetrahydrofolic acid in senile organic mental disorders with depression: results of a double-blind multi-center study. *Aging (Milano)*. 1993;5:63-71.
12. Malouf R, Areosa Sastre A. Vitamin B12 for cognition (Cochrane Review). In: *The Cochrane Library*, Issue 2. Chichester, UK: John Wiley & Sons, Ltd; 2004.
13. Mimori Y, Katsuoka H, Nakamura S. Thiamine therapy in Alzheimer's disease. *Metab Brain Dis*. 1996;11:89-94.
14. Martin DC, Francis J, Protetch J, Huff FJ. Time dependency of cognitive recovery with cobalamin replacement: report of a pilot study. *J Am Geriatr Soc*. 1992;40:168-172.
15. Engelhart M, Geerlings M, Ruitenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer's disease. *JAMA*. 2002;287:3223-3229.
16. 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.
17. Jama JW, Launer LJ, Witteman JC, et al. Dietary antioxidants and cognitive function in a population-based sample of older persons. The Rotterdam study. *Am J Epidemiol*. 1996;144:275-280.
18. Tabet N, Birks J, Grimley E, et al. Vitamin E for Alzheimer's disease (Cochrane Review). In: *The Cochrane Library*, Issue 2. Chichester U.K: John Wiley & Sons, Ltd; 2004.
19. Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements; the Cache County Study. *Arch Neurol*. 2004;61:82-88.
20. Friess E, Trachsel L, Guldner J, et al. DHEA administration increases rapid eye movement sleep and EEG power in the sigma frequency range. *Am J Physiol*. 1995;268(1 pt 1):E107-E113.
21. Huppert F, Van Niekerk J. Dehydroepiandrosterone (DHEA) supplementation for cognitive function (Cochrane Review). In: *The Cochrane Library*, Issue 2. Chichester, UK: John Wiley & Sons, Ltd; 2004.
22. Azuma T, Nagai Y, Saito T, et al. The effect of dehydroepiandrosterone sulfate administration to patients with multi-infarct dementia. *J Neurol Sci*. 1999;162(1):69-73.
23. Thorgrimsen L, Spector A, Wiles A, Orrell M. Aromatherapy for dementia (Cochrane Review). In: *The Cochrane Library*, Issue 2. Chichester, UK: John Wiley & Sons, Ltd; 2004.
24. Holmes C, Hopkins V, Hensford C, et al. Lavender oil as a treatment for agitated behaviour in severe dementia: a placebo controlled study. *Int J Geriatr Psychiatry*. 2002;17:305-308.
25. Ballard CG, O'Brien JT, Reichelt K, Perry EK. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa. *J Clin Psychiatry*. 2002;63:553-558.
26. Van Someren EJ, Scherder EJ, Swaab DF. Transcutaneous electrical nerve stimulation (TENS) improves circadian rhythm disturbances in Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1998;12:114-118.
27. Scherder EJ, Bouma A, Steen AM. Effects of short-term transcutaneous electrical nerve stimulation on memory and affective behaviour in patients with probable Alzheimer's disease. *Behav Brain Res*. 1995;67:211-219.
28. Cameron M, Lonergan E, Lee H. Transcutaneous electrical nerve stimulation (TENS) for dementia (Cochrane Review). In: *The Cochrane Library*, Issue 2. Chichester UK: John Wiley & Sons, Ltd; 2004.
29. Koger SM, Chapin K, Brotons M. Is music therapy an effective intervention for dementia? A meta-analytic review of literature. *J Music Ther*. 1999;36:2-15.
30. Suzuki M, Kanamori M, Watanabe M, et al. Behavioral and endocrinological evaluation of music therapy for elderly patients with dementia. *Nurs Health Sci*. 2004;6:11-18.
31. Kennerly R. An empirical investigation into the effect of beta frequency binaural beat audio signals on four measures of human memory. *Hemi-Sync J*. 14:3; Summer 1996, i-iv.
32. Wang K, Hermann C. Healing Touch on agitation levels to dementia. *Healing Touch Newsletter*. 1999;9:3.
33. Woods DL, Craven RF, Whitney J. The effect of therapeutic touch on behavioral symptoms of persons with dementia. *Altern Ther Health Med*. 2005;11:66-74. □

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