Memory Care Monthly

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Delaying the Onset and Progression of Alzheimer's Disease

In 2001, the Quality Standards Subcommittee of the American Academy of Neurology reviewed the evidence-based medicine published data on the costs and benefits of detecting dementia early. Based on this review, they recommended that persons with mild cognitive impairment (**MCI**) be further evaluated and monitored(1) since MCI greatly increases the risk of developing dementia due to Alzheimer's disease (**AD**) and related disorders.

Currently AD can be delayed for up to 7 years, depending upon how early treatment begins, through a combination of family education, social support, mental and physical stimulation, drug and antioxidant therapy. Because most patients die for other reasons, delaying AD does not prolong life expectancy. However, treating AD reduces overall expenses by decreasing hospitalization and institutionalization rates, diminishing caregiver burden, and helping to control comorbid conditions(2). This is consistent with data from The National Long-Term Care Survey, which suggests that a greater degree of cognitive impairment at time of diagnosis associates with higher total cost of care and longer duration of residence in a nursing home(3).

Main Points

- Preventative therapy delays the onset of AD symptoms by an average of 3.5 years(4), which would reduce AD prevalence by 1/3.
- Early detection and treatment delays progression by up to 3.5 years. Since AD patients are institutionalized for an average of 2.5 years, a 3.5 year delay in AD progression will usually eliminate institutionalization(5).
- At present, total costs of AD are more than $110 billion per year(6). Opportunity costs for the caregiver, such as lost wages, and retirement benefits, exceed $20 billion per year(7).

PREVENTION OF ALZHEIMER'S DISEASE AND RELATED DISORDERS

Non-steroidal Anti-inflammatory Drugs (NSAIDs): 9 of 10 population-based studies have shown that NSAIDs used in low doses for two or more years(8) in persons under 80 years old reduce the chance of developing AD by about 50%(8-13). Low dose means <175 mg aspirin or <500 mg Naproxyn or equivalent dose with other NSAIDs(8). The efficacy of aspirin varies between different studies. Many show about a 30% risk reduction, while the Rotterdam study did not show a risk reduction and the Australian study showed risk reduction comparable to other NSAIDs. Because high and low doses are equally effective, reducing inflammation does not appear to be the mechanism by which NSAIDs reduce risk. Low doses of certain NSAIDs (ibuprofen (i.e., Motrin, Advil); Sulindac; and indomethacin (Indocin)) inhibit the production of ß-amyloid, which is a key component of AD pathology(10).

Data from the Established Populations for Epidemiologic Studies of the Elderly (**EPESE**) showed that persons taking low to moderate doses of NSAIDs performed better on the Short Portable Mental Status Questionnaire than persons not taking NSAIDs or taking high doses of NSAIDs. The magnitude of this effect was estimated to delay the onset of cognitive decline by 3.5 years(4), which corresponds to a 35% reduction in prevalence of dementia due to AD.

Statins: The largest study conducted to date examining the association between statin use and risk of AD was done by researchers from Boston University. They compared the risk factors and medication history between 912 AD patients and 1669 of their normal aging family members. After adjusting for a number of factors, including age, sex, ethnicity, and apolipoprotein E genotype, the relative risk of AD among statin vs. non-statin users was 0.21 (a 79% risk reduction). Other cholesterol-lowering drugs did not show a statistically significant reduction in the relative risk for AD. Further support of this protective effect of statins came from the Canadian Health Study of the Aging(14). 492 Canadians over 65 years old developed dementia after their initial assessment, and were compared to 823 persons who remained normal. After controlling for smoking and hypertension, the relative risk for AD among statin users was 74% less than non-statin users under 80 years old (odds ratio, 0.26; 95% CI = 0.08-0.88). These results are also consistent with a recent meta-analysis of seven studies in the literature, which showed that statin use reduces overall risk of cognitive impairment by 57% (relative risk = 0.43, 95% CI 0.31-0.62), while other lipid lowering agents do not show a statistically significant reduction in risk of cognitive impairment (relative risk = 0.62, 95% CI = 0.28-1.38)(15).

Vitamin E: A 3-year longitudinal within-subject study of 2,889 community residents 65 to 102 years old examined working Memory, short-Term Memory, global mental status and complex task performance. The study found that persons who took Vitamin E: 400 iu/day or higher showed a 1/3 reduction in their rate of cognitive decline compared to those who took little or no Vitamin E(16). Vitamin C and beta carotene showed no effect on rate of cognitive decline. Both dietary sources and supplements of these antioxidants were measured.

DELAYING AD PROGRESSION

Cholinesterase Inhibitors: As discussed below, the long-term studies of the cholinesterase inhibitors, Aricept (donepezil), Razadyne (galantamine) and Exelon (rivastigmine), support their ability to delay AD progression during the dementia stage by 1, 1.5—3, and 2.5—5 years respectively, which underscores the importance of early detection to optimize quality of life. The upper limit on the disease delaying effect is imposed by the average 7 years duration of AD during the dementia stage.

Aricept (donepezil) – Aricept is a weak inhibitor of acetylcholinesterase, and is FDA-approved for mild, moderate and severe AD. After one year of treatment, cerebrospinal fluid levels of acetylcholinesterase increase well above baseline(17), which suggests a time-limited effect of Aricept. An open label study of Donepezil in 133 AD patients for approximately 3 years showed a significant reduction in the rate of cognitive decline as measured by the ADAS-Cog (18). Other studies treating AD patients for up to five years show that after 3 years, the rate of decline approaches that of the natural progression of AD. Overall, there appears to be an approximate 33% reduction in the rate of decline of AD for up to 3 years, which is equivalent to a delay of approximately 1 year.

Razadyne (galantamine) – Razadyne is FDA-approved for mild and moderate AD. In addition to weakly inhibiting acetylcholinesterase, Razadyne allosterically binds to the presynaptic nicotinic acetylcholine receptor, which increases presynaptic acetylcholine release, and increases release of many other neurotransmitters. In experimental animal models, Razadyne blocks programmed neuronal cell death (**apoptosis**), reduces levels of unbound beta amyloid to reduce glutamate mediated excitotoxicity, and reduces cholinergic neuronal cell death. Three year studies of Razadyne in AD patients have demonstrated an approximate 50% reduction in rate of cognitive decline using the ADAS-Cog(19). Overall, there appears to be a 50% reduction in rate of decline in AD for at least three years, which is equivalent to a delay of 1.5 years or longer.

Exelon (rivastigmine) – Exelon is FDA-approved for mild and moderate AD. It is a strong inhibitor of acetyl- and butyryl-cholinesterase that does not develop tolerance for at least one year of treatment(17). Butyrylcholinesterase inhibition may reduce neuritic plaque formation in AD patients(20). In AD patients treated with Exelon for five years, their rate of decline was reduced by an average of 54%(21), which is similar to the reduction achieved by Exelon given to 532 mild to moderate AD patients over 2.5 years(22). Overall, there appears to be a 54% reduction in rate of decline in AD for at least five years, which is equivalent to a delay of 2.5 years or longer.

Memantine (Namenda): Namenda is FDA-approved for moderate and severe AD. Namenda blocks the N-Methyl D-Aspartate (**NMDA**) receptor from permitting calcium ion entry when synaptic activity is relatively low (e.g., -50 mV membrane potential), but is decoupled from the NMDA receptor when synaptic activity increases (e.g., -30 mV membrane potential). This action effectively improves the signal-to-noise level as well as theoretically reduces the chance of glutamate-mediated excitotoxicity, which can trigger programmed neuronal death (**apoptosis**). Reduction of apoptosis via Namenda has been shown clinically in an MR Spectroscopy study of HIV patients (unpublished report, S. Lipton et al.). Whether it also delays AD progression by blocking glutamate-mediated apoptosis or some other mechanism has not yet been proven.

DELAYING INSTITUTIONALIZATION

Cholinesterase Inhibitors (ChEI): Tacrine was the first cholinesterase inhibitor approved to treat AD. A two year study comparing high doses (80 to 160 mg/day) to low doses (<80 mg/day) in mild to moderate AD patients showed that the patients on high doses were 1.75 times less likely to be placed into a nursing home after two years of treatment(23). Time to death did not differ between the two groups. Cholinesterase inhibitor treatments have also shown a reduction in caregiving time. A one year randomized study of donepezil vs. placebo showed that caregivers spent 12 hours per day taking care of AD patients receiving placebo, whereas those receiving donepezil required 10.1 hours of caregiving daily. This difference amounted to an extra 10 weeks of work per year for untreated AD patients(26).

Vitamin E and Selegiline: The Alzheimer's disease Cooperative Study Unit demonstrated that AD patients treated for two years with either selegiline (5 mg BID) or vitamin E (1,000 I.U. [alpha-tocopherol] BID) significantly delayed AD progression, and that vitamin E delayed institutionalization by approximately 1 year(24). Since that time, there has been one meta-analysis showing a 1% increase in overall mortality risk due to d-alpha tocopherol formulations of Vitamin E at doses of 900 IU per day or higher. In foods containing fat, vitamin E is present as a mixture of alpha, beta, gamma and delta tocopherols, and was shown by the Rotterdam prospective study of 5,395 normal aging subjects to reduce AD risk by 20%. In contrast, Vitamin E supplements (predominantly of the d-alpha tocopherol form) had no effect. These findings suggest that the mixed tocopherol formulation of Vitamin E have greatest potential value. Furthermore, because the most commonly available

Vitamin E supplements are d-alpha tocopherol, there is no evidence that mixed tocopherol formulations of Vitamin E are associated with increased mortality risk. At present, the safest recommendation would be to treat AD patients with Vitamin E (mixed tocopherols), 400 I.U. po BID with meals. Vitamin C recycles antioxidants such as Vitamin E to increase their potency, such that 250—500 mg Vitamin C po BID taken with Vitamin E may further improve treatment efficacy.

Caregiver Support: A randomized clinical trial of mild-to-moderate AD patients showed that counseling and educating caregivers combined with support groups delayed time to nursing home placement by about a year. The greatest benefits occurred when patients were mild-to-moderately demented(25). Based on this and other studies, the American Academy of Neurology Quality Standards subcommittee currently recommends short- and long-term programs directed toward supporting and educating family caregivers about AD in order to delay time to nursing home placement.

CONCLUSIONS

From a logical and evidence-based medicine perspective, there is substantial support for disease delaying effects of AD treatment. During the asymptomatic period of AD, which lasts approximately 30 years, identifying risk factors and treating them delays AD symptom onset by an average of 3.5 years. During the symptomatic period of AD (i.e., MCI and dementia stages), a cholinesterase inhibitor should always be included in AD treatment up until the point of hospice care because there are disease delaying benefits to patients and to caregivers. Namenda may ultimately be shown to delay AD progression but the evidence is still at the basic science level. Psychosocial support, and Vitamins C+E or Selegeline provide additional delays in AD progression, with the size of the treatment effect paralleling those of cholinesterase inhibitors.

The challenge of delivering cost-effective and successful dementia healthcare has arrived. The key will be:

- Educating the public about the value of prevention, early detection and treatment.
- Providing physicians with the patient-specific knowledge needed to detect, diagnose, treat and manage each patient to maximize the delay in disease progression.
- Implementing this knowledge delivery within the constraints of today's managed healthcare settings.

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The Next Generation of Alzheimer's Treatments

Currently, 5 drugs in two classes are approved for the treatment of Alzheimer's disease (**AD**) in the USA. Four of them are acetylcholinesterase inhibitors (AChEIs) for mild-to-severe dementia due to AD, and one is an *N*-methyl-D-aspartate (**NMDA**) receptor partial agonist for moderate-to-severe AD. Although these drugs have shown symptomatic improvement in cognition, function and behavior, and more recent studies support a disease delaying effect, they were not targeted to treat what is now the most commonly accepted pathophysiological mechanism of AD—namely, overproduction and/or impaired clearance of beta amyloid 1-42 (**Aß42**).

Some of Aß42-lowering drugs in AD clinical trials are likely to be FDA approved anytime from 2007 to 2009. **Alzhemed** (Neurochem, Inc., Phase III) reduces Aß42 production and brain deposition, and will conclude phase III trials in the first quarter of 2007. **Flurizan** (Myriad Genetics, Inc., Phase III) selectively lowers Aß42 production, thus inhibiting the cascade of paired helical filament and neurofibrillary tangle formation, synapse loss, and neuritic plaque formation, which comprise the triad of AD neuropathology. **AAB-001** (Elan Pharmaceuticals, Phase II) is a monoclonal antibody directed against Aß42. It has been shown in autopsy studies to deplete unbound Aß42 in the brain as well as to remove bound Aß42 from neuritic plaques.

AD animal models show that even the next generation of drugs is unlikely to produce significant reversal of impaired cognitive or functional abilities, and that the primary effect will be on stopping progression. Thus, the critical component to optimally effective AD treatment will be early detection before there is significant clinical dysfunction. Early detection is also important now because currently FDA-approved drugs can delay AD progression by up to 54%. Cognitive impairment is present years before individuals become aware of it—hence the importance of annual memory screening after the age of risk (sometime after 50 years old).

Study Supports use of Dementia Diagnostic Work-up for Patients with Mild Cognitive Impairment

A recent study by Pereira et al. at the University of Minho in Portugal has shown as many as 55% of patients with mild cognitive impairment (**MCI**) had at least one laboratory abnormality including cholesterol, thyroid and glucose abnormalities. This prevalence was similar to that among demented patients (60%).

Current diagnostic guidelines for dementia or Alzheimer's disease include laboratory diagnostic work-ups, yet these work-ups are not well justified for patients with MCI. This finding greatly supports the importance of the use of dementia diagnostic work-ups for patients with MCI.

Reference: Pereira A.F. et al. *JAD* 10 (2006) 53-58.

Survey Highlights Need for Physicians to Raise Awareness about Importance of Memory Screening

A recent study found that only 24% of individuals who worry about their memory share their concern with their physician. The study, conducted by MetLife Market Institute, surveyed over 2,500 individuals who participated in a voluntary memory screening during National Memory Screening Day held in November, 2005 and sponsored by Alzheimer's Foundation of America.

Alzheimer's disease and other memory disorders can be treated and/or delayed if identified early enough. With Alzheimer's disease, the most common cause of memory loss, its progression can be slowed by approximately 50% if treated early. Currently however, most cases of Alzheimer's disease are diagnosed at the moderate or severe stages, which is approximately 7-9 years after the first symptoms. At such late stages, treatments provide limited benefits. This delayed detection has led to the misconception that treatment for Alzheimer's disease has minimum effects but physicians can significantly impact their patient's lives by focusing on early detection of memory disorders.

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