DELAYING THE ONSET AND PROGRESSION OF ALZHEIMER'S DISEASE

INTRODUCTION

Recently, 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 be further evaluated and monitored(1). Mild cognitive impairment is now known to greatly increase the risk of developing dementia due to Alzheimer's disease and related disorders (**ADRD**).

Current methods of prevention and treatment can significantly delay both the onset of symptoms and the progression of Alzheimer's disease (**AD**). Through a combination of family education, drug and antioxidant therapy and lifestyle changes, the effects of this disease can be delayed for three to six years, without extending life expectancy (see below). The result is improved quality of life, reduced costs and a lower need for both formal and informal care for victims of this disease.

According to H. M. Fillit, executive director of the Institute for the Study of Aging, "in the long term, drug therapy for 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).

Unfortunately, dementia is not an easy condition for either families or physicians to deal with. Detection of dementia due to AD and other causes in the primary care setting usually occurs 2 to 4 years after symptom onset, if at all. A recent study found that 75% of moderate and severe dementia cases and >95% of mild dementia cases are not detected in the primary care setting(4). Furthermore, even when dementia is detected, about 75% of physicians do not use the standardized criteria needed to accurately diagnose AD(5).

This difficulty of detecting dementia in primary care settings points to the clear need for services that can assist patients, families and physicians in detecting, diagnosing and treating AD without the need for added time and effort on their part. In spite of the clinical advances in AD diagnosis and treatment, primary care physicians still do not have the mechanisms to apply such knowledge in a useful way within the context of their practice. Medical Care Corporation provides this mechanism. By coupling its automated, interactive, online healthcare system with the most currently available knowledge, Medical Care Corporation consistently facilitates the most favorable clinical results and significant cost savings.

SUMMARY OF MAIN POINTS

- Preventative therapy delays the onset of AD symptoms by 3.5 years(6), which would reduce AD prevalence by 1/3.
- Early detection and treatment delays progression by at least 2.8 years, which usually will eliminate need to institutionalize AD patients(7).

- Delaying onset and progression of AD gives affected persons six more years of good quality life without extending life expectancy(6,7).

- At present, total costs of AD are more than $110 billion per year(8). *Opportunity costs for the caregiver*, such as lost wages, and retirement benefits, exceed $20 billion per year(9).

- Shortening institutionalization by one month saves $2,000(2). Delaying AD by six years would save between $150,000 and $300,000, and allow affected individuals to live out their life at home.

PRINCIPLE FINDINGS

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(10) in persons under 80 years old reduce the chance of developing AD by about 50%(10-15). Low dose means <175 mg aspirin or <500 mg Naproxyn or equivalent dose with other NSAIDs(10). 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(12).

Mild cognitive impairment is now thought to be an early symptomatic stage of AD and other dementing disorders in many individuals. 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(6). Since the prevalence of AD doubles every five years after age 65, the delay of pre-symptomatic AD with current preventive therapy could reduce overall disease prevalence by 35%.

To take advantage of such enormous benefits, the potential complications of preventive therapy need to be minimized and individuals need easy access to the most current preventive measures. Medical Care Corporation's preventive service individually tailors recommended interventions based on medical histories and profiles, and periodically updates these recommendations based on new preventive knowledge. Medical Care Corporation's screening and cognitive monitoring service works in conjunction with its prevention service by screening individuals each time they seek to update their prevention therapy.

Statins

The largest study conducted to date examining the association between statin use and risk of Alzheimer's disease was done by researchers from Boston University School of Medicine. 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(16). 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)(17).

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 an 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(18).

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

Aricept (Donepezil) - In one open label study, Donepezil was given to 133 mild to moderate AD patients for two or more years. Based on cognitive testing using the ADAS-Cog, these patients declined at a rate of 3.3 points/year compared to a rate of 9 points/year based on the natural history of untreated mild to moderate AD patients(19). This study demonstrates a disease delaying effect that persists for at least two years.

Aricept vs. Reminyl – Both Aricept and Reminyl appear to operate by inhibiting acetylcholinesterase. In contrast to Exelon, they inhibit butyrylcholinesterase relatively little. Aricept and Reminyl also bind to the presynaptic nicotinic acetylcholine receptor, which increases presynaptic acetylcholine release, and increases release of many other neurotransmitters. Although Reminyl has been marketed to be unique in its allosteric modulation of the nicotinic acetylcholine receptor, a study funded by the manufacturers of Reminyl suggests otherwise. Aging rats administered either Reminyl or Aricept showed a similar increase in long-term potentiation in the hippocampus during an episodic memory task (Morris water maze). Furthermore, Aricept bound more tightly to the nicotinic acetylcholine receptor than did Reminyl(20). The potential significance of nicotinic acetylcholine receptor binding is that it blocks programmed neuronal cell death (**apoptosis**) in experimental animal models. Also in animal and in vitro models, apoptosis contributes to the neuropathology of AD and other neurologic disorders, including stroke, epilepsy, Parkinson's and others.

To date, the longest open-label study ever done consisted of 763 mild to moderate AD patients who had participated in one of two double blind, randomized, placebo-controlled clinical trials for up to 30 weeks, followed by a placebo washout for three to six weeks, then treatment with Aricept for 144 weeks. Compared to all other groups, the group treated with 10 mg/day during the double blind portion of the study showed consistently better cognitive function for at least 2.4 years (123 weeks as measured by the ADAS-Cog score). Furthermore, patients who had been washed out for six weeks at the end of the double blind study irreversibly declined in cognitive function during this time. When restarted on Donepezil however, AD progression was delayed (ADAS-Cog score), but they never caught up with the group that was only washed out for three weeks.

Exelon (Rivastigmine) - Another study examined 532 mild to moderate AD patients who completed a six month double blind trial of Rivastigmine vs. placebo and then took 6-12 mg/day of Rivastigmine for two more years. These patients showed a decline of 4.2 points, which produced an estimated delay of AD progression of at least 2 years(21).

Exelon vs. Aricept – 382 mild-to-moderate AD patients who had failed Aricept ((80% due to lack of efficacy, 11% due to tolerability problems, 9% both reasons), were switched to Exelon. 56.2% of patients were responders to rivastigmine, as assessed using a global function scale (the Clinicians' Global Impression of Change). Cognitive performance (measured by the Mini- Mental State Examination) and the ability to perform activities of daily living (measured by the Instrumental Activities of Daily Living scale) were improved/stabilised in 48.9% and 57.0% of

patients, respectively(22). These patients either did not tolerate Aricept or were declining on Aricept. Approximately 50% of these patients showed significant stabilization or improvement when switched to Exelon. This study is consistent with the finding that butyrylcholinesterase, which is found inside neuritic AD plaques and may convert Amyloid Precursor Protein to beta amyloid, needs to be inhibited to improve function and slow AD progression.

Memantine (Namenda) -
Memantine has been approved by the FDA for treatment of moderate-to-severe AD. Memantine 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 Memantine 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 INSITUTIONALIZATION

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.

Vitamin E and Selegeline

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).

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 or 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.

ChEI treatment has direct effects on amount of 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).

COSTS OF ALZHEIMER'S DISEASE

In 2000, the estimated number of persons with AD in the USA ranged from 3.1 million to 4.8 million(8). Annual formal and informal costs of caring for AD patients range from $15,360 to $65,885 in year 2000 dollars (midpoint = $40,622), giving an estimated $111.9 billion yearly cost of caring for AD in the USA(27).

The average cost of formal care due to physician and emergency room visits, hospitalization, medications and long-term care, is $27,672, and increases with dementia severity(28). The costs of unpaid caregiving ranges from $10,400 to $34,517 annually, which accounts for 60% of caregiving costs, and can be up to 70 hours per week(9). Lost wages for patient and caregiver plus increased medical costs related to caregiver illness are $50,000/year, or a total of $21 billion annually in the USA(29).

For mild and moderate AD patients, the most significant factor affecting cost of care is the presence of comorbid conditions, with 93% of patients having at least one comorbidity, and 60% having at least three(30). The cost of caring for comorbid conditions in AD are $3000 per year higher than age-matched patients(31). AD patients visit the emergency room twice as often as non-demented, age-matched patients, and are hospitalized an average of 16 days longer, which costs $2500 more per hospitalization(32).

Treatment with ChEI for as little as six months and for as long as two years reduces the chance of being admitted to a long-term care facility by about 50%(23). Even though the cost of ChEI is about $120 per month, the disease delaying effect is cost effective because home care costs only 25% that of formal care in long-term care facilities(2,3). This results in an estimated $2,000 savings per patient for each month that institutionalization is delayed(2).

CONCLUSIONS

From a logical and evidence-based medicine perspective, there is no longer any question whether early detection and treatment is both humane and cost-effective for families, patients, physicians, healthcare providers and payers. The challenge of delivering cost-effective dementia healthcare has arrived. The principle barriers to such delivery 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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