

# Memory Care Monthly

Supporting Healthcare Professionals in Caring for the Aging

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## Preventing Alzheimer's Disease by Delaying Onset

### Treating The Asymptomatic Stage Via Risk Reduction

There are approximately 13 risk factors for Alzheimer's disease and related disorders (ADRD), established by large, longitudinal prospective or large, cross-sectional epidemiological studies<sup>1</sup>. A number of these risk factors, including diabetes type II, hypertension, and hyperlipidemia have been associated with increased beta amyloid 1-42 brain levels<sup>2</sup>, such that the specific combination of Alzheimer's disease (AD) risk factors within a given individual may help explain the variable rate of decline commonly seen across AD patients. Many of these risks can be reduced with appropriate treatment. While a complete discussion is beyond the scope and purpose here, three treatments: non-steroidal anti-inflammatory drugs (NSAIDs), statins, and antioxidants, are discussed here which reduce the risk of developing AD by 35-75%, translating to a delay of AD onset by 3 to 5 years.

### Non-Steroidal Anti-inflammatory Drugs

9 of 10 population-based studies have shown that NSAIDs used in low doses for two or more years in persons under 80 years old reduce the chance of developing AD by about 50%<sup>3-7</sup>. Low dose means <175 mg aspirin or <500 mg Naproxyn or equivalent dose with other NSAIDs<sup>3</sup>. 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. This is consistent with Flurizan's lack of anti-inflammatory activity while being the most potent inhibitor of beta amyloid 1-42 production among all NSAIDs. Eight NSAIDs have been shown to reduce beta amyloid 1-42 brain levels in vivo, among which include ibuprofen, sulindac and indomethacin<sup>6</sup>.

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<sup>8</sup>, which corresponds to a 35% reduction in prevalence of dementia due to AD.

### Statins

The relation between statin use and reducing prevalence of dementia in general, and AD specifically, is complex and probably not related to a single mechanism. Although not always demonstrated, a number of large, well-designed epidemiological studies have shown risk reduction for developing AD. For example, a nested case-control study of 1,364 individuals age 50 years and older selected from 368 primary care practices in the UK found a relative risk of 0.29 (95% CI = 0.13-0.63) for developing dementia among statin users vs. non-users after adjusting for age, sex, history of coronary artery

disease, coronary bypass surgery, hypertension, stroke, smoking and body mass index<sup>9</sup>. The Canadian Health Study of the Aging<sup>10</sup> studied 492 individuals over 65 years old who had developed dementia after their initial assessment, and compared them 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)<sup>11</sup>.

## Supplementary and Dietary Sources of 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<sup>12</sup>. Vitamin C and beta-carotene showed no effect on rate of cognitive decline. Both dietary sources and supplements of these antioxidants were measured.

## Dietary Sources of Vitamins C and E

A well-designed longitudinal, population-based study of AD risk in Rotterdam examined dietary intake of sources of vitamins C and E, which largely consist of fruits and vegetables. They found a 20% risk reduction of AD in persons with a high intake of fruits and vegetables<sup>13</sup>. A similar risk reduction was not seen in persons taking vitamin C and E supplements. One possible explanation why supplements did not reduce AD risk is that most supplements of vitamin E are d-alpha tocopherol, which is less effective in lowering AD risk than mixtures of at least alpha- and gamma-tocopherol<sup>14</sup>. Dietary sources of vitamin E occur as mixed tocopherols, so it remains to be determined whether supplements of vitamin E in the form of mixed tocopherols, with or without vitamin C, can lower AD risk.

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## Japanese Validation Study Supports Accuracy of MCI Screen

A recent study evaluated 63 patients at the Fukuoka University memory clinic using the Clinical Dementia Rating (CDR) Scale to identify a sample of 52 Mild Cognitive Impairment (MCI) (CDR=0.5) and 11 normal aging (CDR=0) patients. Standard diagnostic guidelines were used including the MCI Screen, the Depression Screen, and brain SPECT and/or quantitative MRI. After excluding 7 patients diagnosed with depression, the neuroimaging and MCI Screen results of the remaining 56 patients were compared. Among the 48 MCI patients, 46 were correctly classified by the MCI Screen (96% sensitivity), of which 37 (80%) had specific ADRD etiology diagnosed by neuroimaging. All 8 normal aging patients were correctly identified by both the MCI Screen and the neuroimaging studies. These findings support the use of the Japanese version of the MCI Screen along with SPECT or quantitative MRI in early detection and diagnosis of MCI. Reference: Cho A., Sugimura M., Nakano S., Yamada T. Early Detection and Diagnosis of MCI Using the MCI Screen Test. *The Japanese Journal of Clinical and Experimental Medicine* (2007); 84(8): 1152-1160.

### Research Updates

## PET May be Helpful in Differential Diagnosis of Dementia

According to a recent study of positron emission tomography (PET), using carbon 11-labeled Pittsburgh Compound B (11 C-PiB) may be useful in the differential diagnosis of dementia. Researchers evaluated 10 patients with Alzheimer's disease (AD), 1 with progressive aphasia, 1 with posterior cortical atrophy and 15 healthy controls. 11 C-PiB binding was higher in all of the patients than in controls. Patients with atypical dementia had similar binding patterns as the subjects with AD. However, 11 C-PiB retention was higher on the occipital cortex of the patient with posterior cortical atrophy and was significantly higher on the left cerebral hemisphere in the patient with progressive aphasia. Reference: Ng S. et al. *Arch Neurol.* 2007; 64(8):1140-44.

## Oophorectomy Before Menopause May Increase Risk of Dementia

Two studies conducted at Mayo Clinic found that women who undergo unilateral or bilateral oophorectomy before menopause face almost a 2-fold increase in risk for dementia and parkinsonism when compared with those who retain their ovaries until the age of 50. Furthermore those who received estrogen replacement therapy (ERT) reduced their level of risk and had the same level of risk as those who retained their ovaries. Both studies used data from the Rochester Epidemiology Project, a large long-term integrated database of patient records. The first study included 1,489 subjects who had undergone oophorectomy (676 bilateral and 813 unilateral) and 1,472 age-matched women from the same population who had not had their ovaries removed. The researchers found the risk for dementia and parkinsonism did not differ between woman who had a bilateral or unilateral procedure. The second study included 2,327 patients who had surgical removal of their ovaries (1,252 unilateral and 1,075 bilateral) and 2,368 age-matched women. The study found a comparable level of risk associated with oophorectomy and parkinsonism as the first study. Reference: Rocca W.A. et al. *Neurology.* (e-pub ahead of print: August 29, 2007)

## Silent Strokes Impair Quality of Life

A study using data from Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort evaluated the relationship between silent strokes and an individual's quality of life using the Physical and Mental Component Summary scores of the Short Form 12 (PCS-12 and MCS-12). George Howard, DrPH, from the School of Public Health at the University of Alabama, Birmingham, and colleagues compared the average physical and mental functioning among participant groups symptom-free (n=16,090); history of stroke symptoms but free of stroke/transient ischemic attack (n=3,404); history of stroke (n=1,491); and history of transient ischemic attack (n=818). Compared to subjects without symptoms or a diagnosis of stroke, those with silent strokes had PCS-12 scores that were 5.5 points lower. In comparison, the group that had already had a TIA scored 6 points lower than the group without symptoms. Reference: Howard G. et al. *Stroke.* 2007; 38(9): 2446-52.

## Statins May Prevent Alzheimer's Disease

Dr. Gail Ge Li, at the University of Washington School of Medicine in Seattle and colleagues studied whether antecedent statin exposure is associated with neuritic plaque (NP) or neurofibrillary tangle (NFT) burden in a population-based sample of human subjects. Brain autopsies were performed on 110 subjects, ages 65 to 79 years, who were cognitively normal at enrollment into the Adult Changes in Thought Study.

Neuropathologic findings were compared between statin users with 3 prescriptions of 15 pills of simvastatin, pravastatin, lovastatin, or atorvastatin vs nonusers, based on pharmacy dispensing records. The study found significantly fewer plaques and tangles in brains of those taking statins when compared to those who were not. Reference: Li G. et al. *Neurology* 2007; 69(9): E8-11.

## Transient Symptoms with Infarction on DWI May Increase Risk of Stroke

Shyam Prabhakaran, MD, MS, from Rush University Medical Center, in Chicago, Illinois studied the association between diagnostic category and rate of in-hospital stroke or recurrent TIA among people with TIA with normal DWI results, TSI, and IS. They have reviewed patient medical records between January 2003 and December 2004 with ICD-9 codes for TIA at admission, resolution of neurological symptoms within 24 hours, magnetic resonance imaging within 48 hours, and a discharge diagnosis of TIA or IS. Subjects with transient symptoms and evidence of infarction on diffusion-weighted imaging (DWI) had a higher risk for early recurrent stroke or transient ischemic attack (TIA) than either those with a completed ischemic stroke (IS) or those with transient symptoms and a normal DWI scan. These data suggest that TSI may be a separate clinical entity with unique prognostic implications. Reference: Prabhakaran S. et al. *Arch Neurol.* 2007;64(8):1105-9.

## Donepezil Effective in Late-Stage Alzheimer's disease

Donepezil has been found to improve memory and other cognitive functions in patients with severe Alzheimer's disease (AD) according to new research by Sandra Black, MD, from Sunnybrook Health Sciences Center, in Toronto, Ontario. 63% of patients treated with donepezil had improved or stabilized cognitive function compared to 39% of placebo controls. Memory, language, attention, and name recognition were among the cognitive functions, which improved in those taking donepezil when compared with placebo. The study included 343 subject with severe AD who visited 98 outpatient clinics in the United States, Canada, France, Australia, and the United Kingdom. The 6-month study was a randomized, double-blind, placebo-controlled trial. The Severe Impairment Battery (SIB) was used to assess cognition. At baseline, mean total SIB scores were similar for both groups — 64.6 for donepezil vs 65.2 for placebo. At the end of the study, patients treated with donepezil improved in 5 of 9 SIB cognitive domains: language, attention, memory, praxis, and orienting to name. Reference: Black et al. *Neurology* 2007; 69(5): 459-69.

## DSM-V due out in 2012

On August 8, 2007, the American Psychiatric Association (APA) announced the names of 25 experts who will develop the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). The DSM is the handbook used by professionals to diagnose and classify mental disorders. Publication of the updated version of the handbook is planned for 2012. The current version, DSM-IV was issued in 1994. Since then no new disorders have been added nor have any diagnostic criteria been modified. More information on DSM-V is available at: <http://www.dsm5.org/>



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