Searching for Methods to Detect, Prevent, and Treat Alzheimer's Disease

Alzheimer's disease becomes more prevalent with increasing age, and the world's population is aging at a rapid rate. Unless means are found to prevent or retard the emergence of cognitive impairment in aged individuals, the personal and public health burdens posed by Alzheimer's disease and other cognitive impairment syndromes of the elderly will grow dramatically. This issue of *The American Journal of Psychiatry* includes three contributions that address important facets of this evolving health challenge. Modrego and colleagues provide evidence that magnetic resonance spectroscopy may assist in determining which patients with mild cognitive impairment will go on to develop Alzheimer's disease. Yaffe and coworkers demonstrate that the selective estrogen receptor modulator raloxifene may reduce the development of mild cognitive impairment and other cognitive deficit syndromes in postmenopausal women. Hashimoto et al. examine the important question of whether treatment of Alzheimer's disease with cholinesterase inhibitors reduces disease progression. Taken together, these contributions provide new evidence that technology may assist in identifying patients with Alzheimer's disease before the emergence of Alzheimer's dementia and that medications may help maintain cognition, prevent or delay the emergence of cognitive impairment, and have disease-modifying as well as symptomatic effects.

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Mild cognitive impairment is a syndrome characterized by relatively marked impairment in a single cognitive domain such as memory or moderate impairment in several cognitive domains, but patients continue performing activities of daily living normally and do not meet criteria for dementia (1, 2). Patients with mild cognitive impairment commonly progress to Alzheimer's disease, converting from one diagnosis to the other at a rate of approximately 15% per year on average. Some patients, however, appear to remain in the mild cognitive impairment state for long periods, and occasionally patients recover from mild cognitive impairment to normal cognition (3). Foreknowledge of which patients with mild cognitive impairment suffer from Alzheimer's disease and will progress to Alzheimer's dementia would allow the appropriate application of disease-modifying treatments to prevent further progression at a point when clinical manifestations are limited. Modrego et al. studied the sensitivity and specificity of magnetic resonance spectroscopy in distinguishing patients with mild cognitive impairment that converted to Alzheimer's disease compared with patients who did not progress to Alzheimer's disease over a 3-year follow-up period. An occipital cortex *N*-acetylaspartate/creatine ratio ≤1.61 predicted conversion from mild cognitive impairment to dementia with 100% sensitivity, 75% specificity, a positive predictive value of 83%, and a negative predictive value of 100%. It is surprising that the *N*-acetylaspartate/creatine ratio did not have significant predictive value in voxels derived from the hippocampus or parietal cortex, areas more commonly associated with classic and severe changes of Alzheimer's disease. *N*-Acetylaspartate is considered a surrogate marker of neuronal integrity, and diminished levels of this compound as detected by proton spectroscopy suggest a local decrement in neuronal number. Modrego and colleagues divide their patient

group into converters and nonconverters on the basis of their 3-year observations. A more cautious terminology would be "early converters" versus "early nonconverters," since a substantial number of individuals whose cognitive impairment did not convert within 3 years may go on to develop Alzheimer's disease.

Yaffe and coworkers examined the data from the Multiple Outcomes of Raloxifene Evaluation trial, which included 5,386 women examined for the presence of dementia 3 years after being randomly assigned to receive placebo, 60 mg of raloxifene, or 120 mg of raloxifene. Those receiving the higher raloxifene dose had a 33% lower risk of developing mild cognitive impairment relative to those receiving 60 mg or placebo. There was also a tendency, although not significant, for those receiving the higher dose to have a lower risk of developing Alzheimer's disease or any cognitive impairment syndrome. Raloxifene is a selective estrogen receptor modulator used to prevent and treat osteoporosis. Women with emergent cognitive impairment were generally older and postmenopausal for longer periods of time, were more likely to have had a hysterectomy, were less well educated, drank less alcohol, and had more depressive symptoms at baseline relative to women without cognitive deficits. These observations reinforce an emerging epidemiology indicating that late-onset depression is often a precursor of dementia and that moderate alcohol consumption may reduce the risk of dementia. There is an apparent contradiction between the results of the current study and those of the Women's Health Initiative Memory Study (4), which showed that estrogen plus progestin increased the incidence of dementia in postmenopausal women. However, the current study used a selective estrogen receptor modulator and that may be the critical difference between the two studies. Differences in selection criteria and trial methodology may also contribute to differential outcomes. Potential mechanisms by which raloxifene might defer the onset of cognitive compromise include stimulation of choline acetyl transferase activity in the hippocampus, stimulation of neurite outgrowth, and increasing the numbers of 5-hydroxytryptamine-2A receptors in the cingulate and frontal cortex (5–7). Furthermore, raloxifene has not been associated with adverse cardiovascular or cerebrovascular outcomes that may contribute to cognitive impairment (8). The rate of emergence of mild cognitive impairment or Alzheimer's disease was low in this trial, reflecting the general well-being of the clinical trial participants. The extent to which these apparently beneficial effects of raloxifene can be generalized to other populations awaits further study.

Hashimoto and co-workers investigated the potential disease-modifying effects of donepezil, a commonly used cholinesterase inhibitor. Comparing the rate of brain atrophy as revealed by magnetic resonance imaging measures of the hippocampus taken at 1-year intervals, the investigators compared patients treated with donepezil to historical control subjects assessed identically prior to the availability of donepezil therapy. There was a significant difference between the two groups: the mean annual rate of hippocampal atrophy in the treated group (3.82%) was significantly lower than that in the historical control group (mean=5.04%). The 5% annual decrease in hippocampal volume found by Hashimoto et al. is close to the 4.9% annual change reported by Jack and colleagues (9) in a recent placebo-controlled trial. The authors cite in vitro evidence that muscarinic receptor stimulation decreases beta-amyloid protein production. Nicotinic cholinergic receptor stimulation also appears to protect neurons from degeneration induced by amyloid beta protein (10, 11). It is also possible that the enhanced cognition observed with donepezil therapy may be reflected in relative maintenance of synaptic integrity, which in turn may influence measurable atrophy. The use of historical control subjects in this study requires that the results be regarded as tentative. Historical control subjects appear to have progressed more rapidly than those currently recruited into clinical trials (12, 13). These cohort differences may contribute to the differences reported by Hashimoto et al. A small double-blind, placebo-controlled trial with parallel groups also found a beneficial effect of donepezil on maintenance of hip-

pocampal volume (14). These findings support the reported results. Larger randomized trials with parallel groups will be necessary before final conclusions can be drawn regarding the potential neuroprotective effects of donepezil or other cholinesterase inhibitors.

These three studies provide important new information indicating that advances in technology may assist in identifying patients at risk for Alzheimer's disease. In addition, therapies such as raloxifene may prevent or defer the onset of mild cognitive impairment, thus reducing the number of patients who may progress from mild cognitive impairment to Alzheimer's disease. Cholinesterase inhibitors represent the standard of care for patients with mild to moderate Alzheimer's disease and may have disease-modifying as well as symptomatic effects. These three individual studies represent small but important steps in our march toward more effective prevention and treatment of Alzheimer's disease.

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