Noncholinergic Treatment Options for Alzheimer's Disease

Mary Sano, Ph.D.

Approved treatments for Alzheimer's disease have focused primarily on cholinergic enhancement. New attention, however, is being turned toward preventative treatments such as vitamin E, estrogen, and lipid-lowering agents. Preventative treatments focus on intervening prior to the onset of disease. These treatments are designed to modify the amyloid load. These new approaches require designs that select nonimpaired or minimally impaired populations, using new outcomes with prolonged assessment. The cost of these studies is high, but the potential benefit of delay or prevention of disease is the valuable goal. *(J Clin Psychiatry 2003;64[suppl 9]:23–28)*

The prevalence of Alzheimer's disease, currently about 2 million, is projected to quadruple by 2047.[1] If the onset of Alzheimer's disease could be delayed for 5 years, the estimate may decrease by 50%.[1] Current medications for Alzheimer's disease focus on the symptoms that appear as the disease progresses, but attention is now being turned toward prevention or delay in onset by focusing on intervention prior to disease onset. New treatments such as vitamin E, estrogen, and lipid-lowering agents have the potential to aid in the delay and prevention of Alzheimer's disease. In order to adequately assess the efficacy of these new treatments, new approaches need to be taken toward trial design.

APPROACHES TO TREATMENT

The etiology of Alzheimer's disease can be divided into 3 periods: induction, latency, and detection (Figure 1). Interventions that occur at the earliest stage may promote maximal cognitive capacity. Clinical trials must be specifically designed for each stage.

The model proposed in Figure 1 indicates a period prior to the onset of any symptoms and prior to any evidence of disease pathology at which the individual is at high risk. Interventions at this stage would reduce the likelihood of the initiation of the pathologic process. Study designs would focus on preventing or delaying symptoms. Intervention during the induction period should focus on primary prevention techniques to delay the progress of the disease. The next stage in the model is labeled as the latency period. This is a stage in which pathology may exist but it is mild and symptoms are minimal. In Alzheimer's disease, we consider mild cognitive impairment (MCI) as evidence of the latency stage. MCI is characterized as a stage in which an individual has a severe learning deficit characterized by difficulty recalling newly learned material, with minimal impairment in other cognitive or functional domains. There is evidence that this stage may be associated with aberrant amyloid metabolism as reflected by an increase in amyloid β peptide fragments in plasma and serum t platelets.[2] Intervention at this stage may be considered *secondary prevention*. By the time symptoms of cognitive, behavioral, and functional disturbances are detected, pathology is thought to be apparent. This stage is currently treated with cholinesterase inhibitors, which minimize some of these symptoms, but do not appear to slow the progression of the pathology.

Treatment at the induction and latency stage could have an impact in delaying or preventing the onset of the disease. Brookmeyer et al.[1] demonstrated the potential significance of interventions to delay Alzheimer's disease (Figure 2). Four U.S. studies were used to estimate the prevalence and incidence of Alzheimer's disease in the future. In 1997, the U.S. prevalence of Alzheimer's was 2.32 million, with the percentage of people over the age of 75 with Alzheimer's steadily increasing. According to the authors, in the next 50 years, the annual number of new cases is expected to jump from 360,000 to 1.14 million a year. Reducing the risk would lower the number of cases by 1.15 million after 10 years and 4.04 million after 50 years.

Individuals who are at a high risk for Alzheimer's disease by features such as age, family history of dementia,

From Bronx Veterans Medical Research Development, Bronx, N.Y.

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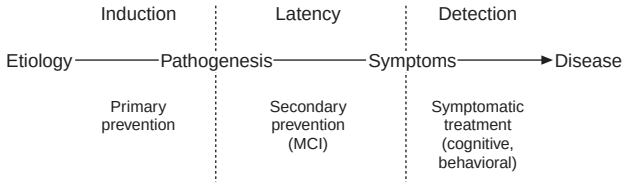
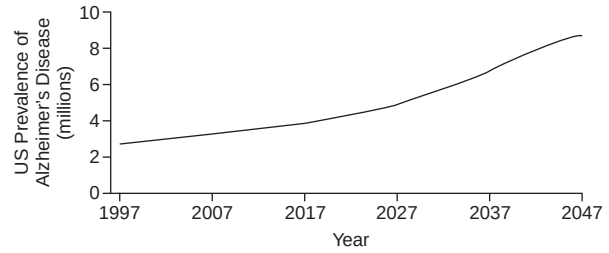
Corresponding author and reprints: Mary Sano, Ph.D., Bronx Veterans Medical Research Development, 130 West Kingsbridge, 151 Room:1F01, Bronx, NY 10468-3904 (e-mail: mary.sano@mssm.edu).

Figure 1. Approaches to Treatment During Different Stages of Alzheimer's Disease



Abbreviation: MCI = mild cognitive impairment.

Figure 2. Potential Impact of Interventions to Delay Onset of Alzheimer's Disease[a]



[a]Adapted with permission from Brookmeyer et al.[1]

or other biological or clinical marker such as memory loss, could be targeted for studies to determine if treatments might substantially delay the onset of illness and, thus, ease the burden of treatment on society.

TRIAL DESIGN

One challenge in developing treatments for the early stages of illness is creating useful methodology. In discussing trial designs for investigating Alzheimer's disease, 2 questions are often raised: how many subjects should be tested and for how long (Table 1)? The sample size is determined by the frequency of the outcome measure in a given population. Sample size generally must increase as the frequency of the outcome measure or symptoms decrease. Trials of patients already diagnosed with Alzheimer's disease, in whom symptoms are likely to progress rapidly, require relatively brief observation periods—about 6 months. As the studies investigate those who are less symptomatic or have slower progression, the study length must increase. Present trial designs, which focus only on symptomatic treatments for cognitive and behavioral impairments, are not likely to be informative to studies of preventative treatments, since those studies require data from large population samples collected over multiple years.

Trial designs for symptomatic treatments compare change in the treated group with change in the placebo group and rely on change scores for efficacy. One challenge for longer trials measuring healthy survival time in Alzheimer's disease is to define meaningful endpoints.[4] In clinical trials for most diseases, the primary endpoint constitutes a definite moment in the progression of the disease, generally remission or mortality. With Alzheimer's disease, death—which may occur several years after diagnosis—may not be a relevant outcome, particularly if it is preceeded by a prolonged period of poor quality of life. Symptomatic treatments have focused on clinical judgement and cognitive performance.[4] These outcomes typically require clinic visits, with in-person evaluations, which can be difficult for Alzheimer's patients as the illness progresses. Many trials that have been conducted on Alzheimer's patients lack endpoint data. When a treatment that delays disease progression is being studied, it may be difficult to establish a measurable outcome; the benefit of treatment may not be observable.

Table 1. Clinical Trials in Dementia: How Many, How Long?[a]

Group	Outcome	Sample Size, N	Duration
Alzheimer's disease	Symptoms change	200–300	6 months
patient	Slow progression		1–2 years
MCI population	Dementia	700–1000	3–4 years
Healthy elders	Dementia	2000–4000	5–7 years

[a]Data from Sano.[3]
Abbreviation: MCI = mild cognitive impairment.

Methodology must be created for studies of treatments that may prevent or slow the disease. Trial designs to assess treatment effects on disease progression can take 2 forms. The first form is to compare the slope of performance over time, as opposed to the actual effect size difference. This outcome is measured repeatedly over a sufficient period of time to make a prediction about the progression. The slopes of the treated and placebo groups can then be compared. The second approach is to use survival analysis, a methodology used frequently in prevention trials of many other diseases. Survival analysis requires the definition of discrete events, such as the conversion to dementia. These trials last several years.

Primary prevention trials, which are conducted in an asymptomatic population, require a large sample size. These trials must be of long duration because they begin before the effects of the disease appear. It can be years before measurable symptoms emerge. In these healthy populations with few symptoms, there is usually a low tolerance for adverse effects among trial subjects. These designs require the risk-benefit ratio to favor low risk.

Treatments at the secondary prevention stage are generally assessable over a shorter period of time. For example, in patients with MCI, over half progress from mild symptoms of memory impairment to dementia within 2.5 years.[5] During this stage, the risk-benefit ratio may swing a little more toward risk, although, in the absence of frank disease, there is still a low tolerance for high levels of risk, including adverse effects.

In trials designed to identify a delay in the time to reach defined endpoints using survival analyses, it may not be possible to make statements about improvements and benefits, as the study is not designed to observe improvements.

PREVENTATIVE TREATMENTS

While Alzheimer's disease is currently treated primarily during the detection period, some studies to slow progression or delay disease have been undertaken. While many preventative strategies have been suggested by prospective epidemiologic and clinical studies, some approaches are being tested in well-controlled randomized clinical trials.

Vitamin E

Vitamin E and other antioxidants have been proposed for slowing the progression of aging and dementia. Antioxidants may slow the deterioration associated with Alzheimer's disease, but not necessarily in the cognitive domain. Trials are ongoing to assess whether or not antioxidants can delay Alzheimer's disease and mild cognitive impairment. Animal studies support a role for antioxidants in the aging brain.[6]

In a multicenter 2-year study[7] of vitamin E and selegiline, patients who had diagnoses of probable Alzheimer's disease of moderate severity were recruited. Participants had to be free of other central nervous system (CNS) diseases, currently not taking psychoactive medication, and residing either at home or in a supervised setting. Three hundred forty-one patients were then randomly assigned to receive 2000 IU/day of alpha-tocopherol (vitamin E), 10 mg/day of selegiline, a combination of both treatments, or placebo. Primary outcome was the time to reach one of the following clinically meaningful endpoints: death, institutionalization, the loss of the ability to perform at least 2 of 3 basic activities of daily living, or a Clinical Dementia Rating scale (CDR) global score of 3. Survival endpoints were acquired through telephone follow-up. However, the secondary outcome measures of cognition, function, behavior, and presence or absence of extrapyramidal symptoms (EPS) required patients to have clinic visits. Problems arose with the acquisition of the secondary outcome data, with more than half the total number of data points missing and fewer than 40% of patients making the final 24-month endpoint visit.

Baseline differences between groups in disease severity as measured by the Mini-Mental State Examination (MMSE) approached significance. However, when baseline MMSE scores were included in analyses as a covariate, a significant delay was seen in the primary outcome measures with vitamin E ($p = .001$), selegiline ($p = .012$), and combination therapy ($p = .049$) versus placebo. Median survival time to the primary outcome event was increased among the vitamin E group by 230 days, the selegiline group by 215 days, and the combination group by 145 days compared with placebo. Cognition changes from baseline were not significantly different among any of the treatment groups.

Further support for the notion that antioxidants might delay Alzheimer's disease comes from an epidemiologic study conducted in the Netherlands.[8] Subjects with a mean age of 67.7 years were prospectively followed. A total of 5395 participants were determined to be nondemented based on a screen using the MMSE, the Geriatric Mental State (GMS) schedule, the Cambridge Examination of Mental Disorders in the Elderly, and an examination by a neurologist and neuropsychologist. At baseline, participants indicated on a checklist all food and drinks they had consumed at least twice a month during the preceeding year and were also questioned about dietary habits, use of nutritional supplements, and prescribed drugs. Patients were followed with the evaluation described above. Dementia was diagnosed based on the DSM-III-R criteria, and the diagnosis of Alzheimer's disease was based on the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.

Participants were followed for an average of 6 years, at the end of which 197 participants developed dementia; of those, 146 were diagnosed with Alzheimer's disease. When adjustments were made for age, sex, and baseline MMSE score only, a significant association between high intake of vitamin C and lower risk of Alzheimer's was seen (rate ratio [RR] per 1 SD increase = 0.82, 95% confidence interval [CI] = 0.68 to 0.99). On the fully adjusted model (adjustments seen with vitamin C plus adjustments made for alcohol intake, education, smoking habits, pack-years smoking, body mass index, total energy intake, presence of carotid plaques, and use of antioxidant supplements), participants who had a higher intake of vitamin E were significantly associated with a lower risk of Alzheimer's disease (RR = 0.75, 95% CI = 0.35 to 0.91) when compared with those taking other antioxidants. Vitamin C demonstrated a borderline significance on the fully adjusted model (RR = 0.66, 85% CI = 0.44 to 1). It was concluded that a high intake of vitamins E and C from food may be associated with a lower incidence of Alzheimer's disease.

Morris et al.[9] observed 815 patients 65 years and older who were free of Alzheimer's disease at baseline. Participants completed the Chicago Health and Aging Project food frequency questionnaire, a self-administered questionnaire. Clinical evaluations of medical history, neurologic examinations, neuropsychological testing, informant interviews, and laboratory testing were also conducted. After a mean follow-up of 3.9 years, 131 patients had developed Alzheimer's disease. Diagnosis of Alzheimer's

disease was made according to the NINCDS-ADRDA criteria. While vitamin E supplements were consumed by 17.3% of participants, no statistical significance was found between vitamin E supplement use and incidence of Alzheimer's ($p = .62$). Vitamin E had a statistically significant dose response in protective effect in the age adjusted model ($p = .04$) compared with vitamin C ($p = .84$) and beta-carotene ($p = .32$). After adjustments were made for age, education, sex, apolipoprotein E (APOE) E4 status, and race, a decreased risk of developing Alzheimer's was associated with an increase in vitamin E from food ($p = .05$) when compared with vitamin C ($p = .88$) and beta-carotene ($p = .37$).

Treatment with antioxidants such as vitamin E potentially can help treat oxidative damage in neuronal cells.[10] Oxidative damage may contribute to neurodegenerative diseases such as Alzheimer's disease.[11] Major reasons for oxidative stress are the combination of low antioxidant potential in the CNS and an increased formation and release of oxygen free radicals by the metabolism occurring as part of the normal aging process. Oxidative stress can cause damage to lipids, proteins, and DNA/RNA; induce amyloid precursor protein; and increase amyloid fragment. This damage can lead to increased antibody deposition, synapse loss, DNA damage, neuronal dysfunction, and death. Treatment with an antioxidant is one strategy that may reduce the damage associated with free radical damage. Despite these positive trends in observational studies, a randomized trial of vitamin E in combination with other antioxidants demonstrated no benefit on cognitive testing in healthy elders.[12]

Currently, several trials are underway with vitamin E. One international clinical trial in adults with Down's syndrome is attempting to determine whether vitamin E can delay the cognitive decline in Down's syndrome patients 50 years of age and older. The pathology from this population is considered similar to the pathology of Alzheimer's disease. Another study examines the benefit in a secondary prevention trial of patients with MCI. It is hoped that information from these trials will provide information not only for adults with Down's syndrome but for patients with Alzheimer's as well.

Estrogen

Epidemiologic, animal behavior, and basic science data suggest that estrogen may have a benefit in delaying dementia. Several prevention studies in healthy women[13,14] have also shown that the use of estrogen can delay or reduce the deterioration seen in the types of cognitive outcome measures that are usually associated with Alzheimer's disease, such as delayed recall and abstract reasoning. However, other trials in people with probable Alzheimer's disease have been disappointing.[15,16]

Jacobs et al.[13] and Tang et al.[14] each have studied the effect of estrogen in delaying Alzheimer's disease. Jacobs et al.[13] assessed 727 women without dementia. Estrogen users were found to have scored significantly higher on the cognitive testing at baseline, especially in areas of verbal recall, delayed recall, abstract reasoning, and naming, than nonusers. These specific measures have been found to predict incident dementia. In the Tang et al. study,[14] 1124 women initially free of Alzheimer's, Parkinson's, and stroke were followed for an average of 2.5 years. Out of this group of women, 156 had been administered estrogen after the onset of menopause. The age at onset of Alzheimer's disease was greater in women who had taken estrogen than in those who had not. The relative risk was significantly reduced in estrogen-taking women as well ($p < .01$).

Studies of conjugated equine estrogens in women with Alzheimer's disease have not had positive results. A study by Mulnard et al.[15] recruited participants from the sites of the Alzheimer's Disease Cooperative Study to test the effectiveness of estrogen in the treatment of women with Alzheimer's. In this 12-month, randomized, double-blind, placebo-controlled, parallel-group design, 120 women participated and 97 completed the trial. Inclusion criteria included a diagnosis of mild-to-moderate Alzheimer's disease with an MMSE score of 14 to 28. These women had a history of hysterectomy, were 60 years of age or older, and did not have major clinical depressive disorder. Patients were randomly assigned to take placebo, 0.625 mg/day of estrogen, or 1.25 mg/day of estrogen. Evaluations were conducted at baseline and again at 2, 6, 12, and 15 months. The primary outcome measure was change in the Clinical Global Impression of Change (CGI-C) scale scores, and secondary outcomes included MMSE, CDR, and Alzheimer's Disease Assessment Scale-Cognitive test (ADAS-Cog). No differences were seen between patient groups on the CGI-C score ($p = .43$), MMSE score ($p = .51$), or ADAS-Cog score. Estrogen failed to improve cognitive/functional outcomes in this study. Further worsening among those taking estrogen was suggested by the CDR scores ($p = .01$) at the end of the trial.

One meta-analysis by LeBlanc et al.[16] sought to determine whether estrogen affects cognition. Only randomized, double-blind, placebo-controlled trials and cohort studies in healthy, postmenopausal women were observed. Results in the area of memory were found to be conflicting. In regards to attention and working memory, no study found that women taking estrogen performed better than women taking placebo. Women who were symptomatic from menopause and were taking estrogen had improved cognitive performance, especially verbal memory tests, vigilance, reasoning, and motor speed, but estrogen did not seem to consistently enhance performance on formal cognitive tests for asymptomatic women.

Most clinical trials have yet to identify the beneficial effects of estrogen in Alzheimer's patients, although most trials examine conjugated equine estrogen and not more

naturally occurring estrogens. Treatment with estrogen may also increase the risk of heart disease and breast cancer. Trials are ongoing in specifically selected healthy individuals who have a family history of Alzheimer's disease but no history of risk factors for cardiac disease, breast cancer, or vascular outcomes that may preclude estrogen therapy.

Lipid-Lowering Agents

Lowering lipids, specifically cholesterol, is associated with a decrease in CNS amyloid deposition in animal models,[17] whereas increased dietary cholesterol increases amyloids. Lowered lipid levels have been associated with a decrease in markers of oxidative stress in rabbits.[18] Inflammatory markers, in particular C-reactive proteins, have been identified in the brains of patients who have Alzheimer's disease. These protein changes are sensitive to lipid load and can be modified by both dietary and pharmacologic lowering of lipid levels. Many studies[17,19,20] have been done to test the efficacy of 3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors (statins), the most commonly used agents to reduce lipids, in patients suffering from Alzheimer's, and other trials are underway.

In one study,[17] mice were used to determine the importance of amyloid β peptide (Aβ) and/or Aβ-containing plaques on the pathophysiology of Alzheimer's disease. Mice were placed on specific diets for 7 weeks. One group of 9 mice were placed on a high cholesterol diet containing 5% cholesterol, 10% fat, and 2% sodium cholate, while 7 mice were fed a basal diet containing only 0.005% cholesterol and 10% fat. Samples were analyzed by a modified sandwich enzyme-linked immunosorbent assay (ELISA) that detects total Aβ. Significant increase in total cholesterol was found in the high-cholesterol–diet mice ($p = .001$) after plasma examination. The mean cholesterol values were 201.66 ± 21.5 mg/dL for high-cholesterol–diet mice and 99.852 ± 9.00 mg/dL for basal-diet mice. The mean values for total Aβ were 347.3 ± 41.30 pmol/g for the high-cholesterol–diet mice and 171.1 ± 23.98 pmol/g for the basal-diet mice. A positive correlation was found between levels of plasma total cholesterol and total Aβ, suggesting that hypercholesterolemia increases Aβ levels in the CNS of the transgenic model for Alzheimer's amyloidosis.

Wolozin et al.[19] conducted a cross-sectional analysis comparing the prevalence of Alzheimer's disease among patients 60 years or older. Data were collected from patient files at 3 different hospitals across the country and a diagnosis of Alzheimer's was made by the NINCDS-ADRDA. Patients were divided into 3 groups: the entire hospital patient population; patients receiving the statins lovastatin, simvastatin, or pravastatin; and patients receiving medications used to treat hypertension or cardiovascular disease. The prevalence of probable Alzheimer's among patients treated with statins was significantly lower ($p < .001$; 60%–73%) than that of the entire patient population and those taking medication for hypertension and cardiovascular disease.

In another study, Jick et al.[20] surveyed patient files collected from the General Practice Research Database for dementia. The patients, all 50 years or older, were grouped according to 3 criteria: all patients with at least 1 prescription for a statin or any other lipid-lowering agent, all patients with a clinical diagnosis of hyperlipidemia who did not receive lipid-lowering drug treatment, or a random sample from the 25,000 people 50 to 89 years old who neither had a diagnosis of hyperlipidemia nor were taking a lipid-lowering agent at any time. Patients with a diagnosis of dementia in each of the 3 groups were identified ($N = 284$) and were randomly matched with up to 4 controls ($N = 1080$) from the base population who met the same criteria in age, sex, practice, and index date of case. Results showed that the risk of dementia among patients suffering from untreated hyperlipidemia ($p = .16$) and those receiving nonstatin lipid-lowering treatments ($p = .91$) was similar to that of the general population. However, patients who had been treated with a prescribed statin showed a 29% reduced risk of dementia ($p = .002$).

Cognitive assessments have been added to clinical trials assessing the benefit of cholesterol-lowering agents on vascular endpoints. While no preventative benefit has been observed with these treatments the trials have been relatively brief or used only end-of-study assessment without controlling for baseline cognitive status. Nevertheless, the notion that lowering lipids could lead to reduced amyloid has biological plausibility, and trials in which cognition is the primary outcome need to be conducted.

CONCLUSION

While the cholinergic agents have introduced hope and some success for the treatment of symptomatic Alzheimer's disease, new mechanisms have been proposed to provide a treatment with a wider benefit and a lower side effect profile at earlier stages of the disease. Currently, there are no pharmacologic approaches to prevention, but it is important to continue preventative studies and not to relegate them to add-on status in clinical trials. Ongoing trials of vitamin E will assess the idea that antioxidants may delay the progress of mild cognitive impairment to Alzheimer's disease, and biological and neurologic data suggest that estrogen may delay dementia. Lowering lipid levels may also decrease oxidative stress and reduce amyloid accumulation, which may have a clinical benefit in the treatment of Alzheimer's disease.

Drug names: conjugated equine estrogens (Premarin), lovastatin (Lovastatine, Atocor, and Mevacor), pravastatin (Pravachol), selegiline (Eldepryl), simvastatin (Zocor).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, the use of conjugated equine estrogens, lovastatin, pravastatin, selegiline, and simvastatin for the treatment of cognition and dementia is investigational.

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