The Search for Better Noncholinergic Treatment Options for Alzheimer's Disease

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Alzheimer's disease is a biological process that involves the disruption of multiple neurochemical pathways. Current treatments for Alzheimer's disease focus on deficits in the cholinergic neurochemical pathway. While newer generation cholinergic agents have a more favorable side effect profile, only a limited, but consistent, degree of efficacy is seen. Treatments are emerging that focus on other areas of neurochemical activity such as oxidative damage, inflammation, glutamatergic neurotransmissions, and serotonergic and dopaminergic pathways. These treatments, supplemented with current cholinergic therapies, may help to ease patients' suffering and caregiver distress.

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It is estimated that over 4 million Americans have Alzheimer's disease.[1] The deterioration of the brain by Alzheimer's involves multiple neurochemical pathways: increased β-amyloid and Tau proteins; dysfunctional apolipoprotein E; degeneration of cholinergic, serotonergic, and dopaminergic neurons; oxidative damage; chronic neuroinflammation; estrogen deficiency; and increased glutamatergic neurotransmission. Currently, cholinergic deficit is the main target of treatments, and cholinesterase inhibitors are the only drugs approved in the United States for the treatment of Alzheimer's disease. While cholinesterase inhibitors may help delay or prevent the breakdown of acetylcholine, a chemical in the brain important for memory and thinking, they cannot cure Alzheimer's disease.[2] A number of alternatives to the cholinesterase inhibitors are being studied. These include *Ginkgo biloba* for oxidative damage and inflammation, nonsteroidal anti-inflammatory agents for inflammation, *N*-methyl-D-aspartate (NMDA) receptor antagonists for normalizing glutamatergic neurotransmission, and atypical antipsychotics and serotonergic antidepressants for improving the serotonergic and dopaminergic pathways.

GINKGO BILOBA

Ginkgo biloba has been used in traditional Chinese herbal medicine for centuries and is a popular antioxidant that some claim helps to prevent damage by free radicals.[3] Ginkgo biloba is commonly used to improve concentration and minimize short-term memory loss due to clogged arteries in the brain.[4] Ginkgo biloba is also thought to aid in treating inflammation among patients suffering from Alzheimer's disease. However, results of studies on the efficacy of ginkgo biloba in the treatment of Alzheimer's disease have not been conclusive.

One randomized, double-blind, placebo-controlled, multicenter study by LeBars and coworkers[5] tested the antioxidant properties of ginkgo biloba among 236 patients aged 45 years or more with Alzheimer's disease and uncomplicated dementia as assessed by DSM-III-R criteria and International Classification of Diseases, 10th revision (ICD-10). Severity was assessed by a Mini-Mental State Examination (MMSE) score of 9 to 26 and a Global Deterioration Scale (GDS) score of 3 to 6. Patients could have no other significant medical conditions such as cardiac disease, insulin-dependent diabetes, liver disease, or chronic renal insufficiency or another psychiatric disorder as a primary diagnosis. To ensure that an unadulterated form of ginkgo biloba was used, the patients were administered either 120 mg/day of the ginkgo biloba extract EGb 761 or placebo for 52 weeks. Primary outcome measures assessed changes in 3 areas: cognitive impairment, using the cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-Cog); daily living and social behavior, monitored by the total score of the Geriatric Evaluation by Relative's Rating Instrument (GERRI); and general psychopathology, using the Clinical Global Impressions of Change scale (CGI-C).

At the end of the 52 weeks, 137 patients completed the study: 78 (50%) of 155 from the EGb 761 group and 59 (38%) of 154 from the placebo group.[5] While mild improvement was observed among the EGb group on the GERRI, the placebo group showed significant worsening

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from baseline (p = .02), which resulted in a statistically significant difference in favor of the EGb group (p = .004). A slight worsening was observed for both treatment groups on the CGI-C (p < .002), and a nonsignificant change in the EGb group but a significant worsening of 1.5 points among the placebo group (p = .006) was seen on the ADAS-Cog. Agitation/nervousness, depression, and emotional lability were cited as the most common adverse side effects among the ginkgo biloba patients, while placebo patients complained more of dizziness and headache.

Another double-blind, placebo-controlled study, conducted by Van Dongen and colleagues,[6] compared 2 doses of ginkgo biloba, administered as EGb 761, with placebo. Patients with DSM-III-R or ICD-10 classified dementia or nondemented patients with age-associated memory impairment (AAMI) were included in the study. Subjects had to be 50 years of age or older, provide written informed consent, have an absence of severe dementia, and have an adequate level of premorbid intelligence (IQ > 80). Entrance criteria were defined as marked-to-moderate dementia (Alzheimer's disease or vascular) as rated by the SIDAM, a German semistructured interview that includes the MMSE and Hachinski Ischemic Score (HIS). Participants were also required to score between 8 and 23 on the Syndrome Kurz Test (SKT) and to demonstrate impaired cognitive functioning on a modified version of the Memory Assessment Clinics Questionnaire (MACQ).

The study consisted of a 2-part randomization strategy: subjects were first randomly assigned either to receive 160 mg/day or 240 mg/day of ginkgo biloba or placebo. After 12 weeks, ginkgo biloba–treated patients were randomly assigned either to continue the previously prescribed ginkgo biloba treatment or to switch to placebo for another 12 weeks. Outcome was measured by digit span tests, a word list, an adapted version of part A of the classic trail-making test, the Sandoz Clinical Assessment Geriatric (SCAG) scale, a 15-item version of the Geriatric Depression Scale, and the Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living. Of 214 patients, 123 patients completed the double-blind study. Intent-to-treat (ITT) analysis showed no difference between the placebo group (N = 44) and either of the ginkgo biloba groups (N = 79) for the entire 24-week period on any measurement.

The studies[5–7] we have to date with ginkgo biloba do not demonstrate clear efficacy among Alzheimer's disease patients. Although the LeBars et al.[5] study demonstrated an improvement among Alzheimer's patients treated with ginkgo biloba, the effect size in the study was small, and could be compared to a non-effective dose of cholinesterase inhibitors.[7] More information is needed in this area before conclusive data can be determined on the efficacy of ginkgo biloba.

NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

Neuroinflammation has also been implicated in the etiology of Alzheimer's disease. Several researchers have investigated the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as a treatment for Alzheimer's disease with mixed results.

In 1997, Doraiswamy et al.[8] analyzed data from 1648 patients with Alzheimer's disease who were classified as users or nonusers of NSAIDs. The data collected from 2 double-blind, placebo-controlled, randomized, 26-week, multicenter drug trials were used to analyze the distribution of baseline ADAS-Cog scores in relation to selected demographic and clinical variables. Women between the ages of 45 and 85 years who met the DSM-III-R criteria for primary degenerative dementia participated in the study. Entrance criteria required each patient to have an MMSE score of 12 to 23, a GDS score of 4 or 5, a score ≤ 16 on the 21-item Hamilton Rating Scale for Depression (HAM-D), and a score ≤ 4 on the HIS. At endpoint, the total mean ADAS-Cog score was significantly (p = .003) lower in the 336 NSAID users than in the 1312 nonusers.

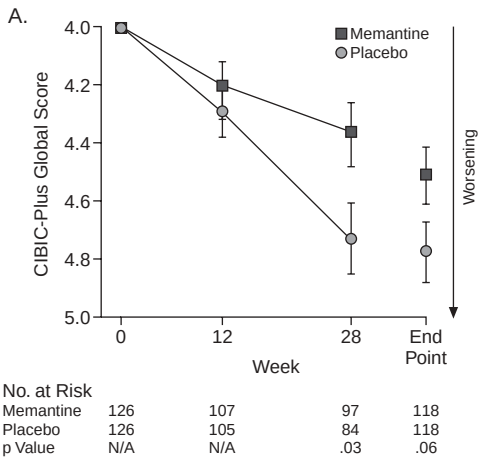
In another double-blind study,[9] a randomized group of 41 patients with mild to moderately severe Alzheimer's disease were administered 50 mg/day of diclofenac with concurrent 200 μg/day of misoprostol or placebo for 25 weeks. Alzheimer's disease was diagnosed according to DSM-IV criteria and an MMSE score of 11 to 25. Primary outcome measures were the ADAS-Cog, GDS, and CGI-C. At the end of the trial, no statistical difference was seen on any of the outcome measures. However, a nonsignificant trend toward less decline was seen in the diclofenac plus misoprostol group.

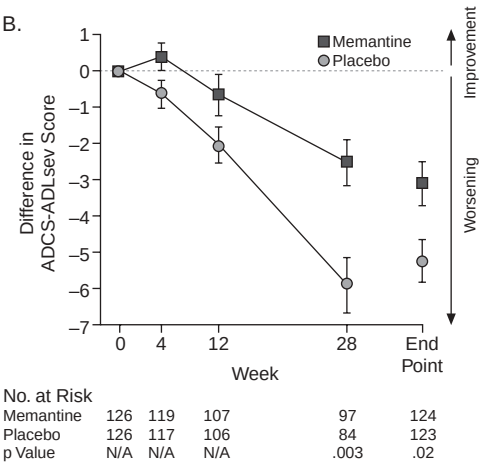
At this point, the use of NSAIDs does not seem very promising in the treatment of Alzheimer's disease. However, nonsteroidal treatments may be helpful in the prevention of Alzheimer's disease.

NMDA RECEPTOR ANTAGONISTS

According to the glutamate excitotoxicity hypothesis, NMDA receptors become overactivated by glutamate, leading to neuronal death due to chronic excitation and cognitive deficits due to a decreased signal-to-noise ratio. It is therefore in the interest of the patient in the early stages of Alzheimer's disease to reduce the effect of glutamate; however, a moderate amount of glutamatergic activity, especially during later stages of Alzheimer's disease, can help facilitate cognitive functioning. Glutamate interacts with the cell during the learning process by changing the signal-to-noise ratio. NMDA receptor antagonists, however, have been known to have undesirable side effect profiles.[10] High affinity antagonist compounds such as phencyclidine (PCP) and MK 801, which have been stud-

Figure 1. Memantine Versus Placebo in Patients With Moderate-to-Severe Alzheimer's Disease[a]





[a]Reprinted from Reisberg et al.[12] with permission.
Abbreviations: ADCS-ADLsev = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory modified for severe dementia; CIBIC-Plus = Clinician's Interview-Based Impression of Change Plus Caregiver Input; N/A = not applicable.

ied for neurodegenerative prevention, are known to block physiologic and pathologic NMDA receptor activity, impairing learning in animal models and having psychotomimetic effects even at extremely low doses. Moderate affinity antagonists may be useful because they can block the pathologic NMDA receptor activity at low doses. These animal data suggest memantine, a low-to-moderate affinity NMDA receptor antagonist, which has been used for many years in Europe for the treatment of patients with various forms and stages of dementia,[11] may be effective as monotherapy or in combination with other treatments in all 3 stages of Alzheimer's disease and lack the impaired learning and psychotomimetic effects of the high-affinity agents.

Human data seem to corroborate these animal studies. Results of a double-blind, placebo-controlled, 28-week, fixed-dose study[12] of memantine for moderate-to-severe Alzheimer's disease were published recently (Figure 1). Of 252 patients who met the entrance criteria and were randomly assigned to take 20 mg/day of memantine or placebo, 181 patients completed the 28-week study. Participants were required to have an MMSE score of 3 to 14, a GDS score of 5 or 6, and a Functional Assessment Stages (FAST) stage of ≥ 6a. At week 28, a statistically significant difference was seen between the placebo and memantine groups on the Clinician's Interview-Based Impression of Change (CIBIC-Plus), the Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory (ADCS-ADL), and the Severe Impairment Battery (SIB). Adverse effects seen with memantine were agitation, urinary incontinence, urinary tract infection, and insomnia. Tariot et al.[13] recently reported that memantine, when used in combination with cholinesterase inhibitors, may be useful in patients with moderate-to-severe Alzheimer's disease.

ANTIPSYCHOTICS AND SEROTONERGIC ANTIDEPRESSANTS

Alzheimer's disease is composed of two main symptoms, cognitive symptoms and behavioral or neuropsychiatric symptoms. Neuropsychiatric symptoms range from delusions and hallucinations to depression and apathy. One study by Lyketsos et al.[14] examined the behavioral disturbances associated with Alzheimer's disease. Participants were 65 years or older and underwent examinations into their medical history and mental status. They also underwent neurologic and brief physical examinations as well as a 1-hour neuropsychological battery. The Neuropsychiatric Inventory was administered to 1002 participants with and without dementia. Participants were rated according to whether they experienced problems in 10 domains over the past month—delusions, hallucinations, disinhibition, irritability, aberrant motor behavior, depression, anxiety, apathy, elation, and agitation/aggression. Participants with Alzheimer's disease cited apathy (28.5% of participants), delusions and agitation/aggression (both 22.4%), depression and irritability (both 20.1%), and aberrant motor behavior (16.8%) as the most severe behavioral disturbances.

Behavioral symptoms can be extremely burdensome on caregivers treating patients with Alzheimer's disease. While cholinesterase inhibitors can be used to treat behavioral symptoms, data[15–17] also suggest that medication that has effects on other neurotransmitters such as dopamine and serotonin can have a clinically significant impact on patients with dementia.

Atypical antipsychotics, which act primarily on dopamine pathways, have been tried for the treatment of behavioral symptoms of Alzheimer's disease. Katz et al.[15] conducted a double-blind study on the effects of risperidone in

625 patients with a DSM-IV diagnosis of Alzheimer's disease, vascular dementia, or mixed dementia. Patients residing in nursing homes or chronic disease hospitals and aged 55 years or more were randomly assigned 0.5 mg/day, 1-mg/day, or 2-mg/day of risperidone or placebo for 12 weeks. Efficacy was measured using the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale, the Cohen-Mansfield Agitation Inventory (CMAI), and the CGI. A reduction of 50% or more in the BEHAVE-AD total score was seen significantly more with 1 mg/day ($p = .02$) and 2 mg/day ($p = .002$) of risperidone compared with placebo. All 3 risperidone groups had significantly better scores on the BEHAVE-AD aggressiveness subscale at week 12; at endpoint, the 1 mg/day and 2 mg/day groups were superior to placebo. On the CMAI, patients treated with 1 mg/day and 2 mg/day of risperidone showed significant improvement over those taking placebo on the verbal, physical, and total aggression scales ($p = .006$ and $p < .001$) at week 12 and endpoint. On the CGI, 1 or 2 mg/day of risperidone reduced the scores from moderate to mild severity, while scores remained at moderate levels with placebo.

Another double-blind trial[16] with an atypical antipsychotic observed the use of olanzapine in Alzheimer patients living in nursing care facilities. One hundred fifty-two patients, who had scored ≥ 3 on any of the agitation/aggression, hallucination, or delusion items of the Neuropsychiatric Inventory-Nursing Home version (NPI/NH), were prescribed placebo or 5 mg/day, 10 mg/day, or 15 mg/day of olanzapine for a period of 6 weeks. The mean age of the patients was 82.8 years. Primary efficacy was measured by the mean change from baseline to endpoint in the sum of the NPI/NH item scores for the core symptoms agitation/aggression, hallucinations, and delusions (the core total score). Significant improvement was seen among the 5-mg/day and 10-mg/day olanzapine groups compared with placebo ($p < .001$). Reduction in caregiver distress was measured by the sum of the occupational disruptiveness scores for agitation/aggression, hallucinations, and delusions (the core disruptiveness score). Significant reduction in core disruptiveness was seen among patients treated with 5 mg/day of olanzapine ($p = .008$).

SSRIs, which primarily affect the serotonin receptors, have also been demonstrated to be effective in treating the behavioral symptoms of Alzheimer's. Pollock et al.[17] conducted a double-blind study of the SSRI citalopram and the antipsychotic perphenazine. Sixty-one patients who met the DSM-IV criteria for Alzheimer's, vascular dementia, or mixed dementia were randomly assigned to 20 mg/day of citalopram, 6.5 mg/day of perphenazine, or placebo for 17 days. Outcome measurements included the Neurobehavioral Rating Scale, UKU Side Effect Rating Scale, and the MMSE. Of the 61 patients who began the trial, 39 completed it. The final total score for the citalopram group was significantly higher than for the placebo group ($p = .002$), but the perphenazine group total score was not significantly higher than the placebo group ($p = .14$) Citalopram and perphenazine showed significant improvement from baseline with respect to agitation/aggression, psychosis, and lability/tension factors. Citalopram showed significant improvement on cognition and retardation factors.

Behavioral symptoms are burdensome not only for Alzheimer patients but for caregivers as well. SSRIs and antipsychotics have been shown to be effective in treating behavioral symptoms among patients as well as reducing caregiver burden.

CONCLUSION

While cholinesterase inhibitors are the only drugs established for the treatment of Alzheimer's disease, new drug treatments may help to alleviate patient suffering. Potential therapeutic interventions for Alzheimer's disease exist for various stages in the progression of Alzheimer's disease. While NSAIDs and NMDA receptor antagonists may provide neuroprotection in the latent stage, ginkgo biloba, antipsychotics, antidepressants, and NMDA receptor antagonists may help at the symptomatic stage. More research must be done before the efficacy of these drug treatments can be adequately assessed.

Drug names: citalopram (Celexa), diclofenac (Solaraze, Voltaren, and others), donepezil (Aricept), misoprostol (Arthrotec, Cytotec, and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), risperidone (Risperdal), rivastigmine (Exelon), sertraline (Zoloft), tacrine (Cognex).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, citalopram, olanzapine, perphenazine, risperidone, rivastigmine, and sertraline are not approved by the U.S. Food and Drug Administration for the treatment of Alzheimer's disease or behavioral symptoms of dementia; diclofenac, ginkgo biloba, memantine, metrifonate, and misoprostol are not approved for the treatment of Alzheimer's disease; and donepezil is not approved for the treatment of the behavioral symptoms of dementia.

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