Pharmacologic Approaches to Cognitive Deficits in Alzheimer's Disease

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This article reviews placebo-controlled studies addressing drug efficacy for the cognitive deficits of Alzheimer's disease. Efforts to compensate for the presynaptic cholinergic deficiency in Alzheimer's disease by pharmacologically inhibiting acetylcholine degradation have been successful in several clinical trials. Two cholinesterase inhibitors are available for Alzheimer's disease, and others most likely will soon be available. Cholinesterase inhibitors represent the only therapy currently approved for the treatment of Alzheimer's disease. The antioxidant drugs alpha-tocopherol (vitamin E) and selegiline have been demonstrated marginally superior to placebo for slowing functional deterioration in patients with moderately advanced Alzheimer's disease. Epidemiologic studies suggest protective effects against Alzheimer's disease from postmenopausal estrogen replacement and nonsteroidal anti-inflammatory drugs. Placebo-controlled studies prospectively evaluating the hypotheses generated by these epidemiologic studies are ongoing. *(J Clin Psychiatry 1998;59[suppl 9]:22–27)*

The efforts to develop treatments to reverse memory and other cognitive deficits of Alzheimer's disease and/or slow cognitive deterioration in this disorder have focused on 3 major strategies. The first has attempted to compensate for the clearly demonstrated presynaptic cholinergic deficit in Alzheimer's disease.[1,2] Several cholinesterase inhibitors, presumably acting by increasing the availability of intrasynaptic acetylcholine, have been therapeutically demonstrated more effective than placebo in several clinical studies. However, results have been modest and adverse effects sometimes troublesome.[3–5] Other cholinesterase inhibitors currently are being studied in advanced clinical trials and may represent further advances in this treatment strategy.[6,7] The second strategy attempts to inhibit endogenous molecules demonstrated to be neurotoxic in experimental models. Recent limited data suggest that the antioxidant drugs alpha-tocopherol (vitamin E) and selegiline may slow functional deterioration in patients with moderately advanced Alzheimer's disease.[8] Extensive efforts to develop compounds that inhibit the production of beta-amyloid (Aβ) remain in the preclinical stages of development. The third strategy relies on epidemiologic data demonstrating that estrogen and nonsteroidal anti-inflammatory drugs (NSAIDs) decrease the risk of developing Alzheimer's disease.[9–11]

CHOLINERGIC ENHANCEMENT STRATEGIES

Cholinergic neurotransmission is involved in memory and other cognitive functions.[12] Blocking cholinergic neurotransmission with agents such as scopolamine impairs cognition,[13,14] and increasing cholinergic activity by preventing enzymatic degradation of acetylcholine[15,16] or administering a cholinergic receptor agonist[17] improves cognition. The loss of cholinergic neurons and markers of brain cholinergic activity in Alzheimer's disease[1,2] suggests that cholinergic enhancement strategies would benefit patients with Alzheimer's disease. An analogous dopaminergic enhancement strategy has proved successful in ameliorating the motor disturbances of Parkinson's disease.

The only clinically successful cholinergic enhancement strategy increases cholinergic transmission by inhibition of acetylcholinesterase, the degradative enzyme for acetylcholine. Acetylcholinesterase inhibitors restore cholinergic deficits at synaptic sites in the brain, resulting in an increase of acetylcholine available to postsynaptic neurons.[18] Although oral cholinesterase inhibitors have not lived up to the high expectations raised by an early study of tacrine by Summers et al.,[19] a number of cholinesterase inhibitors including tacrine, donepezil, and metrifonate have demonstrated modest efficacy in placebo-controlled trials.[4,5,7] Two of these, tacrine and donepezil, are available for treatment of the memory and other cognitive deficits of Alzheimer's disease. Two others, metrifonate and ENA 713 (rivastigmine), may soon be available.

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Tacrine

The first large U.S. trial of tacrine utilized an "enrichment" design.[3] Responsiveness and best dose were determined in a preliminary crossover phase in which patients were randomly assigned to 1 of 3 titration sequences. A best-dose response was defined as the dose of tacrine that resulted in at least a 4-point difference on the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog).[20] Of the 632 patients enrolled in the trial, 215 had a best-dose response and were randomly assigned to receive either placebo or 40 mg or 80 mg of tacrine per day for a 6-week, double-blind phase, followed by a 6-week, sustained, active phase. A mean drug-placebo group difference at the end of the 6-week, double-blind phase of 2.5 points on the ADAS was observed in the tacrine group. There was no difference between the tacrine and placebo groups on the Clinical Global Impression-Change (CGI-C) scale. Twenty-one percent of patients who received tacrine experienced serum alanine aminotransferase (ALT) levels greater than 3 times the upper limit of normal. Except for elevated ALT levels, the most frequent side effects were nausea, vomiting, diarrhea, abdominal pain, and headache.

This initial large-scale tacrine trial[3] was followed by 2 positive parallel-design, double-blind, placebo-controlled studies.[4,21] The first of these was a 12-week study performed in 468 patients at 23 centers.[21] At the end of 12 weeks of treatment, statistically significant differences on the ADAS-Cog and CGI-C were observed in the 80-mg/day group compared with the placebo group. Transaminase elevations of greater than 3 times normal occurred in 25% of patients; all hepatotoxicity was reversible and asymptomatic. Other frequent drug-related adverse events were primarily gastrointestinal: nausea, vomiting, diarrhea, and dyspepsia were common. Skin rash also was reported.

A second, large-scale, double-blind, placebo-controlled, parallel-group trial[4] evaluated 30 weeks of tacrine treatment in 4 treatment groups. Statistically significant mean drug-placebo group differences in ADAS-Cog scores of 2.0 and 2.2 were observed in the 120 mg/day and 160 mg/day groups, respectively. Statistically significant drug-placebo group differences also were found for the Clinician Interview-Based Impression of Change (CIBIC) ratings. Clinically significant (3 times upper limit of normal) ALT elevations occurred in 29% of tacrine-treated patients; 6% of patients experienced ALT elevations greater than 10 times the upper limit of normal. Adverse events included transaminase elevations and gastrointestinal symptoms of nausea, vomiting, dyspepsia, diarrhea, and abdominal pain.

In summary, although higher doses of tacrine have demonstrated modest efficacy in improving cognition in Alzheimer's disease, a high incidence of reversible hepatotoxicity and gastrointestinal adverse effects resulted in poor study completion rates. Drug-drug interactions between tacrine and theophylline, cimetidine, and warfarin can be clinically significant. On the positive side, an analysis of the long-term extension phase of the Knopman et al. study[22] suggests that extended treatment with high-dose tacrine (greater than 80 mg/day) may delay nursing home placement.

Donepezil

Donepezil is a piperidine-based acetylcholinesterase inhibitor. Two randomized, placebo-controlled trials[5,23] have demonstrated efficacy of donepezil 5 mg and 10 mg (the 10-mg dose was marginally but not statistically significantly superior to the 5-mg dose).

The first safety and efficacy study of donepezil was a 12-week, double-blind, placebo-controlled trial followed by a 2-week, single-blind washout.[23] Three daily doses of donepezil were evaluated (1 mg, 3 mg, or 5 mg) and compared with placebo in 161 patients with probable Alzheimer's disease. Statistically significant mean drug-placebo differences of 1.4 and 2.5 points on the ADAS-Cog were observed in the 3-mg and 5-mg groups, respectively, at 12 weeks of treatment. No difference was observed between any treatment group and placebo on the CGI-C. Tolerability was good, with no difference between placebo and any treatment group in reported adverse effects.

A second, large-scale, placebo-controlled trial,[5] to date reported only in abstract form, compared 5 mg and 10 mg daily doses of donepezil to placebo in a 30-week treatment trial. Patients with Alzheimer's disease (N = 450) were randomly assigned to the 3 treatment conditions. Significant drug-placebo group differences were found for both the 5-mg and 10-mg donepezil groups compared with the placebo group on the ADAS-Cog. Although gastrointestinal side effects were more prominent with the 10-mg dose, there was no difference in adverse events between the 5-mg donepezil group and the placebo group.

Low-dose donepezil was better tolerated than high-dose tacrine. Donepezil provides an improved therapeutic index, as well as an increased ease of administration, but no improvement in efficacy compared with tacrine.

Donepezil is started at 5 mg/day in a single-daily dose. Based on tolerability and the clinician's judgment, the dose may be increased to 10 mg/day after 4–8 weeks. Side effects can include gastrointestinal problems, rhinitis, and increased agitation. Often, these side effects subside after a few weeks of treatment. There is no hepatotoxicity, and transaminase or other blood test monitoring is not necessary. No drug-drug interactions were observed between donepezil and cimetidine, theophylline, warfarin, or digoxin, although donepezil is metabolized by the hepatic cytochrome P450 system.

Metrifonate

A third cholinesterase inhibitor, metrifonate, has a unique pharmacokinetic/pharmacodynamic profile that results in changes in cholinergic activity that occur gradu-

Table 1. Comparison of Cholinesterase Inhibitors*

Variable	Tacrine	Donepezil	Metrifonate	Rivastigmine ENA 713	Galantamine
Dosing	4 times/d	Every day	Every day	2 times/d; 3 times/d	3 times/d
Titration	Yes	Yes	No	Yes	Yes
Important side effects	Hepato-toxicity	None	None	None	None

*Based on data from reference 28.

ally, are long-lasting and stable, and are associated with a low incidence of peripheral cholinergic side effects.[24] Tolerability and safety with short-term use have been demonstrated by its worldwide use for the treatment of schistosomiasis since 1962. A double-blind, placebo-controlled trial[7] in 50 patients with probable Alzheimer's disease at a dose of 5 mg/kg per week for 3 months demonstrated a mean drug-placebo group difference of 2.85 points on the ADAS-Cog and significant improvement on a global impression scale with good tolerability. A subsequent study,[25] in which metrifonate was administered once daily, resulted in a favorable pharmacokinetic and safety profile, with little or no accumulation of the drug. Two large, multicenter, randomized, double-blind, placebo-controlled trials[26,27] of once-daily metrifonate treatment followed. In both studies, the mean difference between active drug and placebo groups was approximately 3 points on the ADAS-Cog and +0.3 points on the CIBIC. There were high overall completion rates, and side effects were modest. As with donepezil, metrifonate requires no transaminase monitoring; however, unlike donepezil, metrifonate requires no dose titration.

Other Agents

Other cholinesterase inhibitor agents, including ENA 713, galantamine, and eptastigmine, remain in development. A comparison of features of the cholinesterase inhibitor drugs is provided in Table 1. Several cautions apply to all cholinesterase inhibitors. Their vagotonic activity may exacerbate bradyarrhythmias such as sick sinus syndrome. Cholinesterase inhibitors may increase secretion of gastric acid. They may increase bronchial secretions and should be used with caution in patients with obstructive pulmonary disease. Cholinesterase inhibitors potentiate the effects of succinyl choline and other cholinergic agents. They oppose the effects of anticholinergic agents.

The cholinesterase inhibitor agents provided the first known effective treatments for the cognitive deficits of Alzheimer's disease. Efficacy of these agents is modest. Other cholinesterase inhibitors soon to be available or currently in clinical trials may provide a better therapeutic index than those currently approved.

Muscarinic cholinergic agonists selectively active at postsynaptic M_1 muscarinic receptors provide another approach to cholinergic enhancement in Alzheimer's disease. Such drugs offer the theoretical advantage of avoiding stimulation of inhibitory M_2 muscarinic autoreceptors. A published study of the selective M_1 agonist xanomeline in Alzheimer's disease demonstrates cognitive efficacy compared with placebo.[29] Unfortunately, the magnitude of the cognitive enhancement by xanomeline was no greater and perhaps even less robust than that demonstrated for the cholinesterase inhibitors and was accompanied by significant side effects.

ANTIOXIDANTS

The production of neurotoxic free radicals during oxidative metabolism has been suggested as a mechanism of neurodegeneration in Alzheimer's disease.[30] This neurobiological consideration, coupled with the demonstration that the monoamine oxidase inhibitor selegiline appears to affect positively the course of Parkinson's disease,[31] another late-life neurodegenerative disorder, has stimulated investigation of drugs with antioxidant activity as therapeutic agents in Alzheimer's disease. While it is not clear that the effects of selegiline in Parkinson's disease are mediated via reduction of oxidative metabolism and the subsequent reduction of free radicals, this hypothesis has led to studies of selegiline and other drugs with antioxidant activity such as vitamin E in the treatment of Alzheimer's disease.

Several small, placebo-controlled studies of selegiline in Alzheimer's disease provided some encouragement that this drug may have some therapeutic efficacy in this disease. In an early study,[32] the effects of selegiline at 10 mg/day and 40 mg/day were evaluated in 17 patients with Alzheimer's disease in a double-blind, placebo-controlled serial treatment design. The 10-mg/day treatment produced improved behavior, as measured by Brief Psychiatric Rating Scale (BPRS) measures of anxiety, depression, tension, and excitement. One half of the patients were judged to be globally improved by clinician ratings, with evidence of increased activity and social interaction, and reduced tension and psychomotor retardation. Although most cognitive measures used in this study failed to demonstrate a treatment effect, patients showed significant improvement on the most complex episodic memory and learning tasks. Interestingly, the 10-mg dose appeared more effective than the higher 40-mg dose. Subjects were maintained in each treatment condition for only 4 weeks.

In a much more long-term study,[33] selegiline 10 mg/day was compared with placebo in 39 subjects in a parallel-group designed study. These subjects with Alzheimer's disease had a mild form of the disease as did the patients in the serial treatment design study described above. Again, selegiline was superior to placebo as measured by the BPRS. Although selegiline was not significantly superior to placebo on measures of cognitive function over the 15-month period, a review of the published data reveals

trends for less deterioration in overall function as measured by the Clinical Dementia Rating (CDR) sum of boxes and several tests of cognitive function in the selegiline group compared with the placebo group. Because the power to detect a drug effect was quite small in this study, these results are difficult to interpret.

The most definitive study of selegiline and vitamin E was recently reported by the Alzheimer's Disease Cooperative Study.[8] This study differed from the previous small studies by including subjects with moderate dementia and using as primary outcome measures indices of substantial functional decline such as nursing home placement, increase in severity of disease to stage CDR 3, and loss of major activity of daily living skills. In this large, multicenter trial, both selegiline and vitamin E (2000 IU/day) were superior to placebo in delaying disease progression to these functional endpoints. Interpretation of these encouraging positive results is tempered by 2 findings. First, in a fourth arm of the study, a combined selegiline and vitamin E condition, effects on deterioration tended to be less pronounced than with either vitamin E or selegiline alone. Also, although active treatment delayed progression to functional endpoints, no drug effect on cognitive decline was detected, an efficacy measure required for Food and Drug Administration (FDA) approval of drugs for the treatment of Alzheimer's disease. Both vitamin E and selegiline were safe and well tolerated in this study.

ANTI-INFLAMMATORY AGENTS

The rationale for the use of anti-inflammatory drugs as potential therapeutic agents for Alzheimer's disease is based on both neurobiological observations and epidemiologic studies. The clear presence of inflammatory involvement in the neuropathologic features of Alzheimer's disease has recently been reviewed.[34] Although the role, if any, of the brain inflammatory response associated with Alzheimer's disease lesions remains unclear, it is reasonable to hypothesize that either a primary inflammation or an inflammatory reaction to deposition of abnormal proteins such as Aβ can produce neuronal damage. The roles of such immune factors as produced by activated astrocytes and microglia and the production of inflammatory factors such as the interleukins, S100β, and complement components are current areas of intense investigation in the pathobiology of Alzheimer's disease.

Epidemiologic studies lend further support to a role for a brain inflammatory response in the pathobiology of Alzheimer's disease. An increasing number of epidemiologic studies suggest that prior use of NSAIDs reduces the risk for or delays the expression of Alzheimer's disease.[10] Although retrospective epidemiologic studies do not demonstrate a causal relationship between NSAID use and a decreased risk for Alzheimer's disease, these studies have provided the impetus for prospective clinical trials. One small, placebo-controlled clinical trial of the NSAID indomethacin has been reported.[35] Unfortunately, only 28 subjects completed the study, and the substantial dropout rate was higher in the indomethacin group than in the placebo group. With that in mind, those subjects able to tolerate indomethacin for the duration of the trial showed significantly less cognitive decline than did subjects in the control group.

These neurobiological, epidemiologic, and pilot study data have led to a large, multicenter trial of anti-inflammatory therapy for Alzheimer's disease under the auspices of the Alzheimer's Disease Cooperative Study.[36] In this trial, the anti-inflammatory glucocorticoid prednisone was chosen instead of an NSAID. The rationale for this choice was the greater effectiveness of glucocorticoids as anti-inflammatory drugs and the demonstration that glucocorticoids are effective on inflammatory conditions involving the central nervous system. The dose of prednisone being used in this ongoing trial has been demonstrated to be well tolerated by patients who have Alzheimer's disease. It should be noted, however, that in some animal models, glucocorticoids actually appear to lower the threshold for hippocampal neuronal damage.[37]

ESTROGEN REPLACEMENT THERAPY

Similar to the rationale for anti-inflammatory therapy in Alzheimer's disease, the rationale for the potential therapeutic use of estrogen in Alzheimer's disease is based on neurobiological, epidemiologic, and pilot study data. An increasing number of neurobiological studies demonstrate important roles for estrogen in brain function in experimental models.[38,39] Epidemiologic studies suggest that postmenopausal estrogen replacement therapy reduces the risk for developing Alzheimer's disease in later life.[9,11] In several uncontrolled pilot studies, estrogen has appeared to improve cognitive function in women with Alzheimer's disease.[40,41] A recent, small, placebo-controlled trial also suggests possible efficacy of estrogen in the earlier stages of Alzheimer's disease.[42] These considerations have led the Alzheimer's Disease Cooperative Study to initiate a placebo-controlled trial of estrogen replacement therapy in women with Alzheimer's disease. Use of hormone replacement therapy for more than 10 to 15 years is compatible with a small increase in the risk of breast cancer; however, no increased mortality from breast cancer among estrogen users has been found.[43] Although some studies show a small duration-related risk of breast cancer with estrogen use and a significant increase in endometrial cancer, the latter is virtually eliminated with the addition of a progestin to the regimen.[44]

OTHER APPROACHES

Extracts of the leaf of the *Ginkgo biloba* tree have been used in traditional Chinese medicine for thousands of

years for its believed benefits to the brain. Preclinical studies suggest that such extracts have both antioxidant and anti-inflammatory properties.[45] In a recent study,[46] EGb 761, a standardized concentrated extract of the dried leaves of the *Ginkgo biloba* tree, was evaluated for safety and efficacy in a 52-week, randomized, double-blind, placebo-controlled study in patients with Alzheimer's disease, as well as in a small number of patients with multi-infarct dementia. Subjects taking other cognitively active agents and psychotropic medications at stable doses were not excluded. Subjects were randomly assigned to either EGb 761 40 mg or placebo. Subjects who showed worsening of function or cognitive impairment could be dropped from the study. Of 309 patients included in the intent-to-treat analysis, 202 had assessable data at the 52-week endpoint; only 137 subjects completed the trial. Primary outcome measures were the ADAS-Cog, CGI-C, and the Geriatric Evaluation by Relative Rating Instrument (GERRI), an unvalidated 49-item inventory of patient function completed by the caregiver. Mean total scores on the GERRI range from 1 to 5; the higher the score, the poorer the patient's functioning in the home environment. Very small but statistically significant drug-placebo group differences were found on the ADAS-Cog (1.4 points) and the GERRI (0.14 points). No difference was found in the CGI-C ratings, an efficacy measure required for the FDA approval of drugs for the treatment of Alzheimer's disease. There were no significant differences in adverse events between drug and placebo groups. Despite the fact that *Ginkgo biloba* extracts may have mood-elevating or other behavioral effects, specific behavioral parameters such as mood and agitation were not reported. The very high subject dropout rates and other questions regarding design of this study and interpretation of the results necessitate replication before *Ginkgo biloba* can be considered a treatment for the cognitive deficits of Alzheimer's disease. In addition, safety issues are raised by potential *Ginkgo biloba* effects on blood-clotting mechanisms.

CONCLUSION

It is now clear that cholinesterase inhibitors are effective and safe, but it is equally clear that this class of drugs represents only the first step in the pharmacologic treatment of Alzheimer's disease. Other approaches to enhancing cognitive function in Alzheimer's disease and slowing its progression are currently being evaluated in well-designed studies. It is likely that the number of therapeutic options for treating the cognitive deficits in Alzheimer's disease will continue to increase.

Drug names: cimetidine (Tagamet), digoxin (Lanoxin), donepezil (Aricept), indomethacin (Indocin and others), prednisone (Delta-Dome and others), selegiline (Eldepryl), succinylcholine (Anectine and others), tacrine (Cognex), theophylline (Aminophylline and others), warfarin (Coumadin and others).

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