

New Therapeutic Approaches to Cognitive Impairment

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Therapeutic approaches to the cognitive impairment of dementia are making their way into clinical practice. Clinical pharmacologic approaches toward improvement of cognitive symptoms are discussed, with an emphasis on cholinergic approaches, since they currently appear most promising and since several cholinesterase inhibitors may soon be available for prescribing. As more knowledge is gained about dosing, side effects, and mechanisms of action, these drugs can be prescribed more efficiently. Current research approaches to slowing the rate of cognitive decline are discussed, including the use of antioxidants, monoamine oxidase-B inhibitors, and cholinesterase inhibitors. Drugs that improve cognition may also have effects on behavioral symptoms, severe dementia, and non-Alzheimer's dementia. Evidence suggests that some dementia patients may be particularly responsive to intervention and that other medications may enhance response. Psychosocial interventions may also contribute to prolonging the time to institutionalization. (*J Clin Psychiatry* 1998;59[suppl 11]:8-13)

While treatments to prevent or delay the onset of Alzheimer's disease have yet to be developed, a number of therapeutic approaches to managing the symptoms of dementia are making their way into clinical practice. Although cholinergic deficit is not the only deficit in an illness characterized by progressive nerve cell damage and death, it occurs early in the disease and perhaps to a much greater and denser degree than deficits to other neuronal systems. Pharmacologic agents that increase cholinergic function in the central nervous system (CNS) show efficacy in improving cognitive symptoms, and several new cholinergic agents will soon become available for prescription. Other emerging strategies for treating Alzheimer's disease involve possible slowing of cognitive decline.

Despite our incomplete understanding of the pathogenesis of Alzheimer's disease, there are several potential pharmacologic approaches we can take, including cholinergic approaches. One approach focuses on interfering with the formation of β -amyloid, a major component of the neuritic plaques characteristic of Alzheimer's disease.¹

Another approach aims to reduce the production of hyperphosphorylated *tau* proteins, which are important elements of neurofibrillary tangles, another neuropathologic feature of Alzheimer's disease.² A third approach, based on observations that the cognitive decline in Alzheimer's disease is linked to cholinergic deficits in the brain,³⁻⁵ involves increasing cholinergic function in the brain with cholinergic agents. Other approaches are intended to treat noncholinergic neurotransmitter deficits implicated in Alzheimer's disease, counteract cholinergic atrophy through the use of nerve growth factors or estrogen, limit oxidative damage caused by free radicals through the use of antioxidants or free-radical scavengers, or decrease inflammation through therapy with anti-inflammatory agents (as discussed further in Dr. Kenneth L. Davis's article in this supplement).

PHARMACOLOGIC APPROACHES FOR TREATING COGNITIVE SYMPTOMS

Cholinergic agents are currently the most immediately promising and frequently used experimental treatment for cognitive impairment associated with Alzheimer's disease.⁶ The rationale behind the use of these drugs is the "cholinergic hypothesis," which establishes an association between cognitive decline and cholinergic cell loss in the cortex and other areas of the brain of patients with Alzheimer's disease.³⁻⁵

The classes of cholinergic agents include muscarinic and nicotinic agonists, cholinesterase inhibitors (ChEIs), and indirect modifiers of acetylcholine release. Cholinergic agonists, including xanomeline, milameline, SB202026,

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Presented in part at the symposium "Alzheimer's Disease: From Research to Practice," held May 4, 1996, New York, N.Y., during the 149th annual meeting of the American Psychiatric Association and supported by unrestricted educational grants from Pfizer Inc and Eisai Inc.

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and AF102B, are still in the early stages of development. Although they are potentially promising, it is too early to predict their eventual success. Much of the more immediately promising work, more likely to result in imminent clinical use, is with ChEIs.

The ChEIs include a growing number of agents, ranging from the first-generation ChEIs (tacrine⁷ and physostigmine⁸) to the second-generation ChEIs (donepezil,^{9,10} ENA 713,¹¹ metrifonate,¹² and galantamine¹³), eptastigmine, and others.

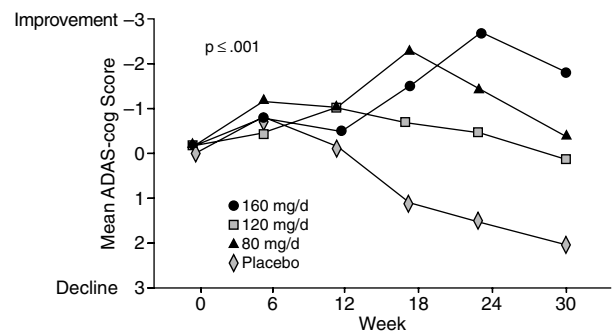
Newer ChEIs tend to be longer acting⁶ and more predictable in their pharmacokinetics. ChEIs differ among themselves in their specificity toward inhibiting acetylcholinesterase (AChE) compared to butyrylcholinesterase and other peripheral cholinesterases. It is theoretically possible that those ChEIs that relatively selectively inhibit AChE may produce fewer peripheral side effects than are associated with other nonselective cholinesterase inhibitors,¹⁴ but this remains to be assessed.

Our understanding of the pharmacologic effects of ChEIs has greatly expanded over the years. As with many medications in which the theoretical rationale initially seemed simple, it may be that these medications may have more profound effects that were not anticipated. Initially, the rationale for ChEI treatment focused on improvement of cognitive symptoms through the intrasynaptic effects of increasing acetylcholine. It was hypothesized that inhibition of acetylcholine degradation led to a greater amount of acetylcholine at muscarinic and nicotinic receptors, resulting in improved cognitive functioning while not affecting the underlying disease. Evidence now indicates that ChEIs also provide neuroprotective effects, perhaps through the activation of nicotinic receptors¹⁵; they appear to enhance neurotrophic regeneration, perhaps through direct stimulation of the muscarinic receptor¹⁶; and they may regulate processing and secretion of amyloid precursor protein (APP) and the production of β -amyloid.^{17,18} Long-term AChE inhibition, by increasing acetylcholine concentrations in the surviving brain synapses in Alzheimer's disease, may activate normal APP processing in such a manner as to slow down or preclude formation of β -amyloid fragments.¹⁶

Tacrine

Tacrine, the first agent approved for the treatment of Alzheimer's disease, and the only drug to be approved for Alzheimer's disease since September 1993, is a centrally and peripherally active, reversible, acridine-based ChEI with a duration of action of 4 to 6 hours. It is nonspecific in that it inhibits AChE, butyrylcholinesterase, and other cholinesterases.⁶ Tacrine is characterized by variable absorption, extensive distribution, good CNS penetration, and nonlinear pharmacokinetics at therapeutic doses, and it exhibits a high degree of dose-dependent activity. It has a therapeutic dosage range extending from 20 mg to 40 mg q.i.d. and requires individualized titration.¹⁹

Figure 1. Dose-Response Effect of Tacrine on Cognition Over 30 Weeks (N = 263)*



*Adapted from reference 19, with permission. ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale Score.

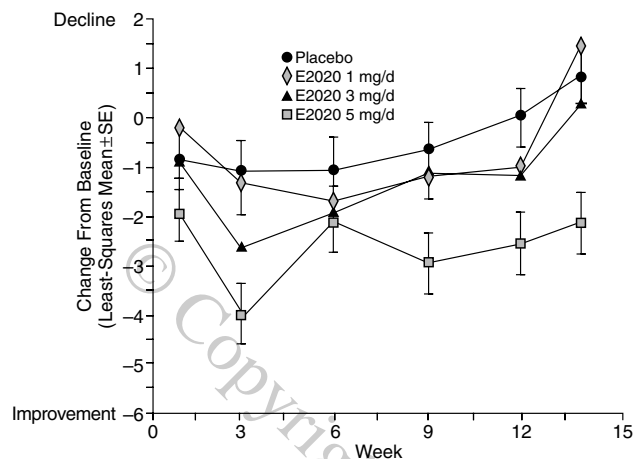
The efficacy of tacrine in the treatment of mild to moderate Alzheimer's disease was established in a double-blind, placebo-controlled, 30-week multicenter trial,¹⁹ in addition to several other trials. In this pivotal trial, data from 263 patients who completed 30 weeks of treatment (out of 663 patients who were randomized) demonstrated that 160 mg/day of tacrine produced statistically significant, clinically observable improvement on objective cognitive tests (such as the Alzheimer's Disease Assessment Scale cognitive [ADAS-cog] subscale and the Mini-Mental State Examination [MMSE]), clinician- and caregiver-rated global evaluations, and quality-of-life assessments (Figure 1). In an intent-to-treat analysis (involving 653 of the 663 patients randomized and followed for 30 weeks, regardless of subsequent treatment), there were statistically significant improvements at a dosage of 160 mg/day in these areas as well.

The primary reason for the substantial withdrawal from the study among tacrine-treated subjects was a 28% occurrence of asymptomatic reversible liver transaminase elevations higher than three times the upper limit of normal, 90% of which was noted within the first 12 weeks of the 30-week study. Gastrointestinal side effects associated with cholinergic excess such as nausea, vomiting, and diarrhea (occurring in approximately 16% of subjects) also were associated with withdrawal from treatment. As detailed in the package insert, patients should be discontinued from tacrine if their transaminases rise over 10 times the upper limit of normal.

Donepezil

E2020, now known as donepezil, is a piperidine-based ChEI that has dose-dependent activity showing greater selectivity for AChE than other cholinesterases and a longer duration of cholinesterase inhibition than tacrine or physostigmine.^{9,20} It is characterized by linear pharmacokinetics at therapeutic doses and has a slow clearance and a 70-hour elimination half-life, which allows it to be given once a day.

Figure 2. Dose-Response Effect of Donepezil HCl on Cognition Over 15 Weeks*



*Adapted from reference 9, with permission.

Results from a 14-week, randomized, double-blind phase 2 trial⁹ involving 160 Alzheimer's disease outpatients indicated that patients receiving 5 mg/day of donepezil showed significantly improved scores on the ADAS-cog, MMSE, and quality-of-life assessments. Moreover, there was a 50% reduction in patients showing clinical decline on a clinicians' impression of change scale. Figure 2 demonstrates the dose-response effect on the ADAS-cog of donepezil on cognition.⁹

Two phase 3 trials examined donepezil 5 and 10 mg/day versus placebo for 12 and 24 weeks, respectively.¹⁰ Over the course of the 24-week trial, patients receiving placebo declined as expected on the ADAS-cog and MMSE cognitive outcome measures, while patients receiving donepezil improved somewhat compared to baseline. Overall, results showed statistically significant benefit in both cognition and clinicians' rated improvement when compared with placebo.¹⁰ There was a trend toward a greater effect of 10 mg/day versus 5 mg/day early in the course of treatment but not at the end of 24 weeks.

As expected, the main adverse reactions were related to peripheral cholinergic effects and were more common with higher doses. Nausea, vomiting, and diarrhea occurred in approximately 10% to 20% of patients and muscle cramping and fatigue in approximately 8% to 10%. However, as with other ChEIs, the effects were generally mild in intensity, short-lived (lasting only a few days), and generally resolved with continued treatment. Approximately 68% of patients completed the 10-mg/day dose, 85% at the 5-mg/day dose, and 80% at the placebo. The drug recently received marketing approval by the FDA and will be available by January 1997.

Since donepezil requires only once-per-day administration and little dosage titration and is not associated with

transaminase elevations, it may be more frequently used than tacrine.

ENA 713

ENA 713 is a pseudoirreversible, carbamate-selective AChE subtype inhibitor. It is characterized by its binding and inactivation of AChE and is not metabolized by the hepatic microsome system.¹¹ In earlier studies, it significantly improved cognitive test scores in patients with dementia. As with other ChEIs, it shows dose-dependent activity, with higher doses generally being associated with greater improvement. ENA 713 is currently undergoing phase 3 testing; results should be available soon.

Metrifonate

Metrifonate is an organophosphorus-based prodrug that is converted to dichlorvos, an irreversible CNS ChEI with somewhat greater selectivity for AChE than for other cholinesterases.²¹ Historically, it has been used to treat schistosomiasis.²² Metrifonate has linear pharmacokinetics and a wide dosage range of 40 to 300 mg/day. Clinical response may be linked to levels of cholinesterase inhibition rather than to drug concentration, and, because of its irreversibility, it has a red blood cell AChE inhibition half-life of 50 days.¹² Side effects occur with relatively low frequency at levels of red blood cell cholinesterase inhibition of 75%.

In the first multiple-dose trial conducted over a prolonged period of time, 20 patients with probable Alzheimer's disease were administered single oral doses of 2.5, 5.0, 7.5, and 15 mg/kg/week of metrifonate over three phases with durations of 2 weeks, 1 month, and 1 to 3 months.¹² Substantial improvements in ADAS-cog scores were observed with the 5-mg/kg weekly dose. This dosage produced more than 80% inhibition of plasma and red blood cell cholinesterase, with only minor side effects. Phase 3 trials are under way.

In a 3-month, double-blind trial using a weekly dosing regimen, metrifonate-treated patients showed significant improvements on cognitive and clinical measures, and, in an 18-month open follow-up, showed deterioration of only 1.68 points/year on the MMSE.²³ Phase 3 trials are ongoing.

PHARMACOLOGIC APPROACHES FOR SLOWING THE RATE OF DECLINE

One aspect of treatment gaining interest is the attempt to slow the rate of decline of both cognition and functional activities, thereby preserving patients' quality of life and autonomy.⁶ Methods that have been proposed for slowing the progress of Alzheimer's disease symptoms generally involve altering processes of neuronal death with antioxidants, monoamine oxidase inhibitors (MAOIs), anti-inflammatory agents, cholinergic agents, estrogens, or neurotrophic factors.

Antioxidants and Monoamine Oxidase-B Inhibitors

Evidence from animal and human studies suggests that oxidative mechanisms may play a role in the loss of at least some neuronal systems.^{24,25} The brain is known to be susceptible to oxidative stress, which can result in a "neurodegenerative" cascade involving disruption of DNA, damage to membranes, and neuronal death.²⁶ Regional losses of glutamine synthetase activity, an enzyme particularly sensitive to mixed-function oxidation, were observed in patients with Alzheimer's disease but not in control subjects, suggesting a specific brain vulnerability to age-related oxidation and an excess of oxygen-based free radicals or a decrease in endogenous antioxidant activity.²⁷ Among the antioxidants considered to have a potential neuroprotective effect are MAOIs,²⁸ vitamin E, ascorbic acid, coenzyme Q,²⁹ and idebenone.

It has been proposed that chronic administration of low-dose selegiline, a selective MAOI type B, would reduce the concentrations of free radicals and other neurotoxins.²⁹ Selegiline has been shown *in vitro* to reduce the oxidative stress associated with the catabolism of dopamine.³⁰ In addition, data on the early treatment of Parkinson's disease with selegiline suggest that, in at least a subgroup of patients with dementia of the Alzheimer type, chronic administration of selegiline might prevent or retard degeneration of systems vulnerable to the oxidation of exogenous neurotoxins.²⁶

Selegiline and vitamin E were used in a recently completed, 2-year, multicenter, placebo-controlled clinical trial conducted by the National Institute on Aging and Alzheimer's Disease Cooperative Study (NIA/ADCS) units to assess their effects alone or in combination on the rate of decline in patients with Alzheimer's disease.³¹ The study was designed in the following way: patients with moderately severe Alzheimer's disease were randomly assigned to selegiline, vitamin E, the two in combination, or placebo. The patients were followed until they reached certain endpoints: death, institutionalization, loss of two of three activities of daily living, or an entire level decrease on a dementia rating scale. Survival time (rather than cognitive functioning) was the primary measure. This is a different type of approach than simply measuring cognitive function. The results of this interesting study were published in early 1997.³²

Cholinesterase Inhibitors

The rate of cognitive decline in patients with Alzheimer's disease also appears to be slowed by the use of ChEIs, which may have neuroprotective as well as other effects. Such neuroprotection has been suggested by data on subjects with Alzheimer's disease who were treated with tacrine and monitored from the end of a 30-week, double-blind study for at least 2 years.³³ Time to institutionalization was longer for subjects maintained on higher

therapeutic doses of tacrine compared with those receiving low-dose tacrine.

An apparent reduction in patient deterioration also has been observed by others.^{15,34-36} Results from these studies indicate that cognitive deterioration in patients with Alzheimer's disease who received a ChEI was slowed by several months to a year when compared to historical data.

Anti-Inflammatory Agents

There is substantial evidence supporting the hypothesis that inflammatory processes and immune systems are implicated in the pathology of Alzheimer's disease.³⁷ Inflammatory and immune reactions are evidenced by observations of reactive microglial cells surrounding senile plaques and astrocytes, and the consequent production of inflammatory cytokines. Two of these cytokines, interleukin-1 and interleukin-6, promote the synthesis of APP, which then may be processed to potentially neurotoxic β -amyloid.

The unexpectedly low prevalence of Alzheimer's disease in patients with rheumatoid arthritis, a condition treated with nonsteroidal anti-inflammatory drugs (NSAIDs), supports the theory that NSAIDs confer protection against Alzheimer's disease.^{38,39} Case-control twin studies have also demonstrated that NSAIDs provide a protective effect.⁴⁰ The potential role of NSAIDs in Alzheimer's disease is supported by results from a controlled trial⁴¹ that indicated stable cognitive function in the indomethacin-treated group and declining function in the placebo group. A long-term treatment trial with low-dose prednisone (10 mg/day) is under way, sponsored by the NIA/ADCS.

PHARMACOLOGIC APPROACHES TO TREATING OTHER SYMPTOMS IN DEMENTIA

Drugs that improve cognition also may be efficacious in treating behavioral symptoms, severe dementia, and non-Alzheimer's dementia. For example, there is evidence from open case series that tacrine improved behavioral symptoms in patients with Alzheimer's disease.⁴² Findings from other studies suggest that ChEIs improve behavioral symptoms in Lewy body variants, severe dementia, and depression.

POTENTIAL PREDICTORS OF RESPONSE TO ChEIs

The clinical and biological heterogeneity of Alzheimer's disease leads to heterogeneous responses to ChEIs.⁴³ In addition, ChEIs are quite frequently underdosed⁴³ because of their variable pharmacokinetics and pharmacodynamics and their peripheral cholinergic effects. There also appears to be a therapeutic window, or curvilinear relationship, in which the effects of these

agents appear to be strongly linked to the amount of cholinesterase inhibition that is achieved. The most significant factors in achieving therapeutic response with ChEIs appear to be sufficient dosages, plasma drug concentrations, and extent of cholinesterase inhibition.⁴³ Ideally, one should be able to see a correlation between AChE inhibition and cognitive improvement. These factors need to be investigated and will help to explain the variability of response.

PSYCHOSOCIAL INTERVENTIONS

In addition to drug therapy, psychosocial intervention has been shown to postpone the institutionalization of patients with Alzheimer's disease. Mittelman and colleagues⁴⁴ reported a randomized clinical trial in which intensive psychosocial intervention reduced the need for patients with Alzheimer's disease to be institutionalized by their caregivers compared with usual clinical care. In this study, 206 caregivers were randomly assigned either to the treatment group, which received individual and family counseling, support-group participation, and consultation as needed, or to the comparison group, which received routine clinical care. By the end of 1 year, the treatment group had less than half as many institution placements as the control group, although there was no difference in death rate.

SUMMARY

New therapeutic approaches to treating patients with Alzheimer's disease focus on improving symptomatology over approximately a 6-month period and slowing disease-progression. Treatment with ChEIs is currently the most promising therapy, especially with the introduction of newer agents. Emerging evidence suggests that ChEIs may have disease-modifying effects appearing to slow the rate of disease progression, but such a claim has to be subjected to controlled clinical trials. The most important predictors of response to ChEIs appear to be adequate dosages, plasma drug concentrations, and degree of cholinesterase inhibition. Current multicenter studies compare the effects of vitamin E and selegiline in slowing the progression of Alzheimer's disease, and anti-inflammatory drugs are being assessed over 1 year for their effect on cognition.

Drug names: dichlorvos (Atgard and others), donepezil (Aricept), indomethacin (Indocin and others), prednisone (Delta-Dome and others), selegiline (Eldepryl), tacrine (Cognex).

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