New Cholinergic Therapies: Treatment Tools for the Psychiatrist

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This article reviews the current status of therapy with acetylcholine-enhancing compounds in the management of patients with Alzheimer's disease. The focus is on pivotal articles investigating the role of cholinergic augmentation strategies, including precursor loading and acetylcholinesterase (AChE) inhibitors, in the management of cognitive and noncognitive symptoms of Alzheimer's disease. Precursor loading strategies have been for the most part unimpressive. By contrast, studies with AChE inhibitors—tacrine and donepezil—have been promising. For patients in whom hepatotoxicity and gastrointestinal side effects were not problematic, tacrine improves cognitive performance and selected secondary psychiatric symptoms and significantly delays nursing home placement. Donepezil, recently approved for use in mild to moderate Alzheimer's disease, appears to be less toxic and better tolerated than tacrine. It improves performance on cognitive testing and, in one preliminary investigation, demonstrated a sustained drug effect over several years. Therapy with AChE inhibitors provides modest significant symptomatic improvement in patients with mild to moderate Alzheimer's disease.
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THE CHOLINERGIC LESION IN CONTEXT

Recent findings in the study of Alzheimer's disease have challenged traditional views of the pathophysiology of the disorder. Rather than viewing Alzheimer's disease as a disorder of late life, we now think that in most cases its onset is earlier in life. Alzheimer's disease also has a strong genetic component. Genetic abnormalities have been identified as risk factors in 30% to 60% of Alzheimer's disease cases.[1] There are multiple lesions associated with the disease process. These include amyloid deposition, a tissue inflammatory response, and massive destruction of cholinergic neurons. Because of its complex, multifactorial nature, it is likely Alzheimer's disease may begin years, and possibly decades, before the clinical expression.

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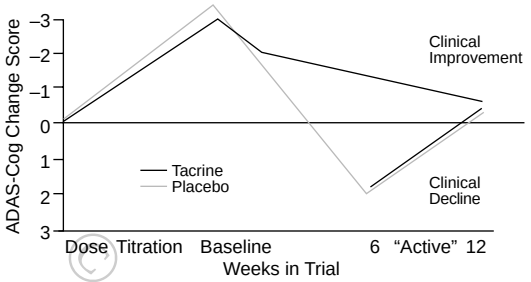
The cholinergic lesion in Alzheimer's disease has been carefully articulated over the last several decades. Davies and Verth[2] described deficiencies in the cholinergic enzyme—choline acetyltransferase—in postmortem samples of Alzheimer's disease patients. This was followed years later by the pivotal observation that cholinergic cell bodies in the nucleus basalis of Meynert are destroyed by the disease process, leading to a deficiency of the neurotransmitter acetylcholine.[3] During this same period, several clinical reports showed that drugs that blocked acetylcholine caused memory deficits in normal subjects[4] and later in normal elderly groups.[5]

These observations led to new experimental treatment strategies for Alzheimer's disease. All had the goal of increasing amounts of available acetylcholine in brains of Alzheimer's disease patients. These included precursor loading strategies (e.g., lecithin), postsynaptic agonists, and acetylcholinesterase (AChE) inhibitors. Of these, the commercially available cholinesterase inhibitors (tacrine, available clinically in 1993, and donepezil, available in 1997) have proven to be the most successful.

NEW CHOLINESTERASE THERAPIES: AVAILABLE, EFFECTIVE TREATMENT TOOLS FOR THE PSYCHIATRIST

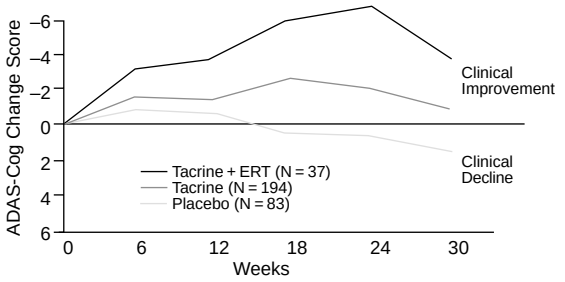
Before the cholinergic treatment strategies are reviewed, ergoloid mesylates, though not specifically a cholinergic strategy, should be mentioned in a historical context. This agent was the leading treatment strategy prior to the development of the cholinergic compounds. It was in-

Figure 1. Mean Change in Total ADAS Score Over the Course of Tacrine Study*



*From reference 9, with permission. Abbreviation: ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive portion. All patients received tacrine and placebo during the placebo-baseline phase. Patients who received placebo during the double-blind phase were switched to tacrine therapy during the sustained active phase.

Figure 2. ADAS-Cog Subscale Scores at Week 30 for Intent-to-Treat (ITT) and Treatment Completers*



*From reference 10, with permission. p Values are for tests of trends comparing tacrine plus estrogen replacement therapy (ERT), tacrine, and placebo. In the ITT analysis, women receiving ERT and tacrine (N = 37) had significantly better response at 30 weeks than women not receiving ERT who were assigned to placebo (N = 83; p = .02) or to tacrine (N = 194; p = .01).

troduced in 1960 for treatment of senile mental deterioration. After decades of use, there remains considerable controversy about its mechanism of action and whether it works at all in Alzheimer's disease patients. The European experience has been with doses considerably higher than those approved for use in the United States. Very high doses of ergoloid mesylates (up to 9 mg/day) have been shown in some clinical studies to have a modest clinical effect. By contrast, the typical dose in the United States is 3 mg/day. Overall, the general clinical experience is that these higher doses are no more effective than placebo.[6]

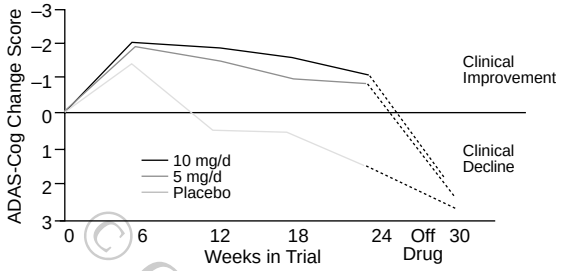
Acetylcholine precursor loading strategies were among the first of the new approaches. Of these, lecithin was the most thoroughly investigated. Preclinical studies had shown that lecithin increased brain acetylcholine levels in animals. This, coupled with its low toxicity, made it an ideal candidate as a precursor loading strategy. Unfortunately, most well-conducted studies showed little, if any, cognitive improvement.[6–8] Also, because lecithin is essentially fish oil, patients taking higher doses of lecithin complained that they smelled like fish. Choline, a related precursor strategy, had similar adverse effects.

The cholinesterase inhibitor strategy began with early trials using physostigmine. Several investigators[6–9] found that it had a positive effect on cognitive measures in Alzheimer's disease. Unfortunately, the half-life is 20 minutes to a maximum of 2 hours, making it impractical in the real world. Gastrointestinal side effects were common in doses that enhanced cognition. Currently, 2 cholinesterase inhibitors have been approved by the Food and Drug Administration (FDA) for use in Alzheimer's disease patients. Both tacrine and donepezil have positive effects in the symptomatic management of Alzheimer's disease.

Tacrine is an amino acridine compound that was shown to result in symptomatic improvement in patients with Alzheimer's disease. Figure 1 provides the main results of the collaborative study used to achieve FDA approval.[9] Using the Alzheimer's Disease Assessment Scale, cognitive portion (ADAS-cog, a standard rating instrument in clinical drug trials) as the principal outcome measure, patients were enrolled into either a slow titration schedule using tacrine or a placebo treatment group. Over the 6-week trial, patients receiving placebo worsened. Patients receiving tacrine also worsened, but at a slower rate. At the end of the trial, there was a significant difference (4 points on the ADAS) between drug-treated patients and the placebo group. After the placebo phase, the placebo-treated patients were treated with tacrine. These patients then performed as well as those patients in the original treatment group. A recent, retrospective study[10] found that postmenopausal women who, in addition to tacrine, took estrogen replacement therapy, performed better over a 30-week trial period than did patients taking tacrine alone (Figure 2). This observation was recently supported by data from the Baltimore longitudinal study of aging.[11] Four hundred seventy-two postmenopausal women were followed for 16 years. In those women taking estrogen replacement therapy, the incidence of Alzheimer's disease was diminished by 50%.

Tacrine has proven beneficial in managing some of the behavioral disturbances in Alzheimer's disease.[12] Behavioral disturbances typically identified as secondary psychiatric symptoms showed some improvement in tacrine-treated patients. These symptoms included apathy, hallucinations, disinhibition, and aberrant motor behaviors. Tacrine had a significant impact on time to nursing home placement in patients able to tolerate doses in excess of 80 mg/day.[13] In those patients, the time to nursing home placement was delayed by approximately 500 days. Unfortunately, amino acridine compounds are associated with significant hepatotoxicity, and tacrine proved no exception. Approximately 30% of patients develop significant elevations in liver function tests in the doses that are clinically effective.[6] This results in the need to monitor weekly liver function tests in patients for at least the first 16

Figure 3. Mean Change From Baseline in ADAS-Cog Scores During 24-Week Treatment With Placebo or Donepezil (5 mg/day and 10 mg/day).*



*From reference 14, with permission. Weeks 24–30 are a drug washout period.

Table 1. Donepezil Side Effects*

Side Effects	Placebo (%)	5 mg/day (%)	10 mg/day	
			1 Week (%)	6 Weeks (%)
Nausea	6	5	19	6
Diarrhea	5	8	15	9
Insomnia	6	6	14	9
Fatigue	3	4	8	3
Vomiting	3	3	8	5
Muscle cramps	2	6	8	3
Anorexia	2	3	7	3

*Data from reference 14.

weeks. Those patients developing liver function test abnormalities are usually advised to discontinue treatment.

The most recent addition to commercially available medications is donepezil. This compound has several advantages over its predecessors. First, the pharmacokinetics are quite predictable. The usual treatment doses are 5 and 10 mg/day. Five mg/day causes approximately 60% to 70% AChE inhibition; 10 mg/day causes approximately 80% to 90% AChE inhibition.[4] It also appears to have greater specificity for CNS acetylcholinesterase. Donepezil is very potent as an AChE inhibitor, but has relatively little effect on butyrylcholinesterases. Tacrine and physostigmine, by contrast, inhibit both acetyl- and butyrylcholinesterases. The lack of specificity of tacrine for CNS acetylcholinesterase may partially explain the higher rate of peripheral side effects encountered with tacrine as opposed to donepezil. Donepezil is metabolized through hepatic glucuronidation via the P450 system. The relevant enzymes are the 2D6 and 3A4. The half-life is 70 hours, allowing for once-daily dosing (compared to q.i.d. dosing for tacrine), a distinct advantage in this elderly population. Figure 3 provides the data from the pivotal study used to secure FDA approval.[14] Four hundred fifty patients were assigned to 1 of 3 treatment groups: placebo, 5 mg/day, and 10 mg/day. Patients were treated for 24 weeks, followed by a 6-week drug washout period. The placebo-treated group worsened over the course of the study. Patients receiving 5 and 10 mg/day were, at the conclusion of the 24-week period, significantly better than placebo-treated patients. While the 10-mg/day group did better than the 5-mg/day group, this difference was not statistically significant.

Of considerable interest is the side effect profile for donepezil (Table 1). There was little difference between placebo and 5 mg/day in overall side effect profile. Side effects were greatest in patients who started on 10 mg/day. Even these patients rarely experienced sustained adverse effects. After 6 weeks on 10 mg/day, the overall side effect profile was only slightly greater than for 5 mg/day or placebo. Because of this, the usual recommendation is to start with 5 mg/day and then, after 4 to 6 weeks, to increase the dose to 10 mg.

One critical question is how long will the drug provide a therapeutic effect. To draw from the clinical experience with ergoloid mesylates mentioned above, most physicians are understandably reluctant to prescribe any medication continuously without some evidence that it is effective. In 1 open-label study, donepezil was administered for 2 years to a small cohort of patients (Tune LE et al., unpublished data, 1998). Compared to the predicted rate of decline in Mini-Mental State Examination (MMSE) scores (2–4 points per year) from previously published data on the natural course of Alzheimer's disease, 7 of 8 donepezil-treated patients performed better over the 2-year study period. Donepezil-treated patients showed evidence of progression of illness, but at a rate parallel to the predicted decline of the untreated patients. At the end of the 2-year study period, they performed consistently better on the MMSE. The final answer to this question is forthcoming, as several long-term trials are coming to completion.

It is important to make the distinction between symptomatic and structural medication effects. A symptomatic treatment provides some relief for the period of time the patient takes the medication. It has no effect on the underlying disease process. Donepezil and tacrine are both symptomatic treatments. Structural medications, by contrast, alter the course of illness. We are in the early stages of investigation of medications that may have this effect (e.g., estrogen, antioxidants). None are currently indicated in Alzheimer's disease. Neither donepezil nor tacrine has been shown to affect the structure of the illness.

FUTURE STRATEGIES: BEYOND THE CHOLINERGIC STRATEGY

The cholinergic lesion in Alzheimer's disease is only one piece of the disease puzzle. Another neurotransmitter abnormality found less consistently involves norepinephrine and serotonin. Zubenko et al.[15] studied postmortem samples of Alzheimer's disease patients, including patients who had a clinically significant depression at some point in the course of the illness. Significant decreases in norepinephrine content were found in several brain re-

gions in the depressed compared to the nondepressed demented patients. Zweig et al.[16] found similar abnormalities for both norepinephrine and serotonin. In all, these data suggest a possible biochemical subclassification of Alzheimer's disease patients into those with and without deficiencies in catecholamines. Catecholaminergic abnormalities may well contribute to some of the behavioral disturbances seen in Alzheimer's disease patients—insomnia, depression, appetite disturbances, agitation, and psychosis. The relationship between catecholamine abnormalities and behavioral disturbances is only now being articulated. These observations from postmortem studies provide support for many of the symptomatic therapies currently in use in Alzheimer's disease patients. For many patients, the combination of donepezil or tacrine plus antidepressant medications may provide the greater symptomatic benefit.

Recent data support the use of nonsteroidal anti-inflammatory drugs (NSAIDs) possibly in a combination strategy with cholinesterase inhibitors and other symptomatic treatments. Briefly, the rationale is as follows: microglia work in the brain in a manner much like the peripheral immune system. One hypothesis from preclinical studies is that activated microglia may produce interleukins that accelerate the process of converting amyloid precursor protein to the toxic β-amyloid. This, in turn, deposits into affected cells, leading to neuronal degeneration. Nonsteroidal antiinflammatory agents may slow this process and, in turn, structurally affect the course of illness. Rogers et al.[17] compared the antiinflammatory agent indomethacin to placebo and found that indomethacin-treated patients performed slightly better than placebo patients on cognitive testing after 6 months of treatment. Data from the Baltimore longitudinal study on aging show that people taking NSAIDs (primarily ibuprofen) had a significant reduction in the development of Alzheimer's disease.[18]

Other current research strategies include the use of monoamine oxidase (MAO) inhibitors and antioxidants. In Alzheimer's disease, there is a significant increase in MAO-B activity.[19] One hypothesis is that this increase causes an increase in the oxidative deamination of monoamines. The resultant increase in free radicals may predispose exposed cells to injury. MAO-B inhibitors have been compared alone and in combination with the antioxidant vitamin E in patients with Alzheimer's disease.[19] Each compound—vitamin E and selegeline (MAO-B inhibitor)—proved successful, compared with placebo, in delaying progression of disease.[20] The combination of vitamin E and selegeline was no more effective than each compound administered separately.

To summarize, there are now 3 possible treatment strategies for the near future. The first involves symptomatic interventions. Acetylcholinesterase inhibitors—tacrine and donepezil, with many others soon to follow—are the clearest examples. Catecholaminergic interventions (e.g., serotonin selective reuptake inhibitors [SSRIs]), quite likely in combination with AChEs, especially for management of allied behavioral treatments, fit this category. The second strategy—prevention and structural modification approaches—include estrogen replacement strategies in postmenopausal women, nonsteroidal antiinflammatory agents, high-dose vitamin E alone or in combination with the MAO inhibitor selegiline, and selegiline alone. The third strategy—preventive therapy/gene therapy—is a goal for the future.

This of course could lead to more extensive combination treatments for Alzheimer's disease: cholinesterase inhibitors in combination with catecholaminergic compounds (e.g., SSRIs) plus estrogen plus NSAIDs plus antioxidants. These could eventually be offered to individuals at risk of illness. Reiman et al.[21] recently found that at-risk, asymptomatic individuals who carried 2 alleles for the APOE4 gene displayed characteristic changes on positron emission tomography images long before the expression of the illness. Perhaps some of these approaches could soon be offered to individuals who are clearly identified as being at very high risk for developing Alzheimer's disease. Much of the current research is to identify additional early, presymptomatic markers of illness (e.g., markers for cell death, inflammatory response, amyloid deposition).

One goal is to accurately identify individuals prediagnostically or presymptomatically. By using these combinations of treatment strategies, we may then be able to "push back the curve" so that the symptomatic onset is delayed. In this sense, donepezil "pushes back" the clock by at least 40 weeks. Perhaps, by combining estrogen, NSAID, and antioxidants, in presymptomatic or at least early cases, we can push the clock back even farther.

Drug names: donepezil (Aricept), ergoloid mesylates (Hydergine and others), ibuprofen (Motrin and others), indomethacin (Indocin and others), selegeline (Eldepryl), tacrine (Cognex).

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