

Medical Treatment of Alzheimer's Disease: Past, Present, and Future

Brian R. Ott, MD

Due largely to the success of cholinesterase inhibitor drugs in recent clinical trials, Alzheimer's disease (AD) can no longer be regarded as "untreatable." In this review I will reflect on previous concepts about the medical treatment of AD before discussing the therapeutic options. Although the cholinesterase inhibitors have indeed met with "modest" success in partially alleviating cognitive, behavioral, and functional impairments, these symptomatic treatments fail to inhibit the disease process itself. This limitation in efficacy has led to a nihilistic attitude toward this class of medication on the part of some practicing physicians. Therefore, the conclusion of this review will look forward to the potential of new therapies to slow or interrupt the disease process and provide a complementary and more effective treatment approach.

THE PAST

With the advent of tricyclic antidepressants, many elderly patients with early memory loss and mood disturbance were treated for these combined target symptoms with some success. Largely anecdotal experience in this population led to the concept and term "pseudodementia," popularized in the late 1970s to describe those in whom both mood and cognition seemed improved with treatment of late life depression. Reversal of cognitive target symptoms was felt proof positive that the patient was experiencing a mood disturbance rather than an early degenerative dementia. This dichotomous paradigm was challenged by subsequent studies of "pseudodementia" patients followed beyond three years, which found that the majority went on to express the classical signs and symptoms of AD.¹ We now know that it is not uncommon for patients with prodromal AD to have associated mood disturbances. For example, depression may be a grief reaction by patients aware of their deficits or reflect their fear and anxiety over the prospect of getting AD. Hence, pseudodementia may

best be regarded as a "pseudodiagnosis."

Reifler and colleagues in 1989 conducted a revealing study of the treatment of depressive symptoms in AD.² In this randomized double-blind, placebo-controlled trial of imipramine, depression was shown to improve equally for drug and placebo-treated patients. Cognition measured by the Mattis Dementia Rating Scale revealed significant impairment in the drug-treated group compared to placebo. This study demonstrates that depression is a reversible symptom in dementia; however, the benefits of medication are equivocal. Furthermore, the negative anticholinergic effects of tricyclic agents mitigate against their use in this vulnerable group of patients, in whom there is uniformly an already existent cho-

linergic neurochemical deficit.

The availability of selective serotonin reuptake inhibitors, (SSRIs) with their wider safety margin and lack of anticholinergic side effects, spurred a rebirth of the ubiquitous use of antidepressants in dementia patients. Although clearly having less adverse effects on cognition than older agents, the small number of dementia trials of SSRIs with agents such as fluoxetine thus far have revealed similar equivocal results regarding efficacy. Clinical experience, though, suggests that when properly selected, some patients with AD clearly benefit from antidepressant medication for relief of depression and anxiety symptoms. A therapeutic trial of one or more agents is reasonable, so long as the physician is willing to discontinue

Table 1. Cholinesterase inhibitors: Pharmacologic characteristics

	Tacrine	Donepezil	Rivastigmine	Galantamine
Year available	1993	1996	2000	2001
Brain selectivity	No	Yes	Yes	Yes
Reversibility	Yes	Yes	Yes/Slow	Yes
Chemical class	Acridine	Piperidine	Carbamate	Phenanthrene alkaloid
Enzymes inhibited				
Ache	Yes	Yes	Yes	Yes
BuChe	Yes	Negligible	Yes	Negligible
Nicotinic receptor modulation	No	No	No	Yes
Doses per day	4	1	2	2
Initial dose (mg./day)	40	5	3	8
Maximum dose (mg./day)	160	10	12	24
Given with food	No, unless nausea occurs	No	Yes	Yes
Frequency of nausea / vomiting	28%	11% / 5%	47% / 31%	24% / 13%
Plasma half-life (hours)	2-4	~70	~1	~6
Elimination pathway	liver	liver	kidney	50% kidney 50% liver
Metabolism by CYP450	Yes	Yes	Minimal	Yes

Abbreviations: AchE=acetylcholinesterase; BuChe=butyrylcholinesterase; CYP450=cytochrome P450

Table 2. Cholinesterase inhibitors: Comparative effects on cognition from phase III clinical trials

	Daily dose (mg.)	Change in ADAS-cog	
		Score vs. placebo*	Reference
Tacrine	40/80	~2.0	Farlow et al., 1992 ⁸
	120/160	2.0/2.2	Knapp et al., 1994 ⁹
Donepezil	5/10	2.5/2.9	Rogers et al., 1998 ¹⁰
	5/10	1.3/2.8	Burns et al., 1999 ¹¹
Rivastigmine	1-4/6-12	0.2/2.3	Rosler et al., 1999 ¹²
	1-4/6-12	1.7/3.8	Corey-Bloom et al, 1999 ¹³
Galantamine	16/24	3.3/3.6	Tariot et al., 2000 ¹⁴
	24	3.9	Raskind et al., 2000 ¹⁵

* last observation carried forward

ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive subscale

analysis at end point favored haloperidol for the primary behavioral outcome, and the dropout rate was higher for risperidone.

A major breakthrough in our approach to the treatment of AD has been the development of cholinesterase inhibitor therapy. Deficiency in cholinergic neurotransmission is seen uniformly in patients with AD, as a result of degeneration of the nucleus basalis of Meynert and other associated nuclei in the basal forebrain. Administration of anticholinergic drugs such as scopolamine provides a model for experimentally induced amnesia. This line of evidence led to what has been referred to as the "cholinergic hypothesis" for AD, which holds that the dementia symptoms of AD are directly related to the deficit in cholinergic neurotransmission.

The repeated success of cholinesterase inhibitors in clinical trials for AD supports the cholinergic hypothesis. As a class these medications produce clinically relevant improvements not only in cognition, but also daily living functions and behavioral problems like apathy and psychosis that are noticeable by caregivers. Tables 1 and 2 compare the four drugs for prescription use.

Recent studies have demonstrated that the symptomatic benefit of such medication extends to three years, and probably beyond. Such long-term effects are likely to translate into significant socioeconomic benefits (e.g., delay in nursing home placement). While clinically meaningful, it must be recognized that this treatment approach fails in large part due to several factors: 1) Cholinergic therapy treats the downstream results of neurodegeneration and has little to no meaningful effect on pathogenesis. 2) AD is not a solitary neurotransmitter deficiency disorder. In fact, other deficits in ascending noradrenergic, serotonergic, and dopaminergic systems are probably of much more relevance in producing the disabling and most important behavioral problems of the disease. 3) Cholinergic therapy theoretically should become ineffective as time progresses and more synapses are lost through degeneration processes.

Research has now shifted toward ways of interrupting neurodegeneration

medication when there is no convincing evidence of benefit.

A similar quandary exists regarding the use of minor and major tranquilizers. The benzodiazepines are falling out of favor for managing anxiety and mild symptoms of agitation, since it has been recognized that such medications may produce paradoxical confusion and agitation as well as predispose to risk for falls in the elderly. Neuroleptic agents are also frequently accompanied by unwanted side effects such as confusion, somnolence, hypotension, and extrapyramidal signs such as parkinsonism. Among the major tranquilizers used to treat psychosis, there has been no best choice drug. In a 1990 meta-analysis of antipsychotic drug trials in dementia,³ Schneider concluded that 18% of dementia patients benefitted from neuroleptic treatment compared to placebo. Furthermore, no single drug appeared more efficacious or safer than another.

Because of tranquilizers' frequent side effects, behavioral management programs are preferred as the first line of treatment for agitation. Trazodone is often used as well as a first-line medication to reduce agitation and treat sleep disturbance. Recently a well-designed clinical trial carried out by dementia experts in the Alzheimer's Disease Cooperative Study (ADCS) ex-

amined the comparative efficacy of haloperidol, trazodone, behavioral management techniques, and placebo for the treatment of agitation in AD.⁴ The sobering finding was that none of the four drugs available was more effective than placebo.

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THE PRESENT

In recent years several new antipsychotic drugs have come to market, commonly described as "atypical," because of their lower propensity to cause extrapyramidal side effects compared to older drugs. Among the atypical antipsychotics most commonly prescribed are risperidone, olanzapine, and quetiapine. Unfortunately, in the elderly demented population even these drugs can produce unwanted side effects. Whether or not these drugs are better than the older agents is debatable. For example, in a recent study comparing risperidone to haloperidol, risperidone was reported to be the more effective treatment,⁵ even though the

in AD in hopes of slowing, stabilizing, or even preventing disease. Antioxidants may help in this manner. In a study from the ADCS which examined high dose vitamin E (1,000 units twice daily) and selegiline in patients with moderate AD treated over two years, those receiving vitamin E or selegiline (but not the combination) appeared to have a significantly slower rate of decline in their function.⁶ Subsequently, the combination of vitamin E and a cholinesterase inhibitor have become standard and relatively safe therapies for AD at the present time.

THE FUTURE

Current clinical trials of drugs for AD are employing agents that we hope will interrupt neurodegeneration to slow disease progression as well as improve function by a mechanism other than cholinesterase inhibition. For example, memantine, approved for use in Germany, is undergoing phase III trials in this country. It acts by reducing neuronal overstimulation by potentially damaging excitotoxic neurotransmitters. Another drug in a somewhat earlier stage of development is leteprinin (Neotrofin®). Leteprinin enhances the brain's own nerve growth factors in a manner that may restore function and reduce cell death over time. Whether or not these agents will succeed in clinical trials remains to be seen. Approval of one or more of these newer agents would likely complement the use of cholinesterase inhibitors and perhaps lead to more meaningful and sustained benefits over time.

As physicians have become more adept at accurately diagnosing AD at progressively earlier stages, interest has shifted to those with mild memory loss but not frank dementia as a target group for early intervention. Persons with "mild cognitive impairment" (MCI) are at risk for conversion to AD at a rate of between 10 and 20% each year. The ADCS is conducting a three year longitudinal study to determine whether early intervention with donepezil or high dose vitamin E, compared to placebo, can have a significant impact on reducing the conversion to dementia for this at-risk group. To date this important study is more than half way completed. Another ongoing prevention study is the Women's Health Initiative

Memory Study, which examines whether estrogen replacement therapy reduces a woman's risk of developing dementia. It has been estimated that if one could delay the onset of dementia by five years, the worldwide prevalence of AD would be halved.

Great progress has been made in understanding the molecular biology of AD. One major theory of the pathogenesis of AD is the "amyloid hypothesis," which holds that deposition of amyloidogenic protein in the AD brain is a seminal event that leads to a cascade of neurotoxic processes terminating in plaque formation, loss of synapses, and ultimately cell death. If this is true, then one should be able to prevent or halt AD by interrupting this cascade. At present drugs which block secretase enzymes that cleave the beta-amyloid precursor protein into amyloidogenic fragments, are in their early stage of development.

Another approach to interrupting amyloid neurotoxicity, which has received a great deal of press lately, is vaccination against beta-amyloid.⁷

This approach in transgenic mice has shown dramatic results, indicating complete blockage of beta-amyloid formation and even partial reversal of established plaques. So far, the injections in humans have been found to produce an immune response; however, phase two clinical trials of the vaccine were recently suspended when 15 of the patients developed "central nervous system inflammation."

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Brian Ott, MD, is the Director of the Memorial Hospital Alzheimer's Disease and Memory Disorders Center, and Professor, Department of Clinical Neurosciences, Brown Medical School.

CORRESPONDENCE:

Brian R. Ott, MD
Neurology Department
Memorial Hospital of Rhode Island
111 Brewster Street
Pawtucket, RI 02860.
phone: (401) 729-3757
fax: (401) 729-3101
e-mail: Brian_Ott@mhri.org

