

REVIEW ARTICLE

DRUG THERAPY

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Alzheimer's Disease

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ALZHEIMER'S DISEASE IS A PROGRESSIVE AND FATAL NEURODEGENERATIVE disorder manifested by cognitive and memory deterioration, progressive impairment of activities of daily living, and a variety of neuropsychiatric symptoms and behavioral disturbances. Prevalence studies suggest that in 2000 the number of persons with Alzheimer's disease in the United States was 4.5 million.¹ The percentage of persons with Alzheimer's disease increases by a factor of two with approximately every five years of age, meaning that 1 percent of 60-year-olds and about 30 percent of 85-year-olds have the disease.² Without advances in therapy, the number of symptomatic cases in the United States is predicted to rise to 13.2 million by 2050.¹ The cost of caring for patients with Alzheimer's disease is extraordinary; annual expenditures total \$83.9 billion (in 1996 U.S. dollars).³ These figures underscore the urgency of seeking more effective therapeutic interventions for patients with Alzheimer's disease.

Treatment of Alzheimer's disease includes five major components: neuroprotective strategies, cholinesterase inhibitors, nonpharmacologic interventions and psychopharmacologic agents to reduce behavioral disturbances, health maintenance activities, and an alliance between clinicians and family members and other caregivers responsible for the patient. Treatment requires accurate diagnosis and increasingly is based on an understanding of the pathophysiology of the disease.

DIAGNOSIS

Alzheimer's disease is the most common form of dementia in the elderly. Dementia is commonly recognized with use of the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).^{4,5} The diagnosis of Alzheimer's disease is most often based on the criteria developed by the National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA),⁶ according to which the diagnosis is classified as definite (clinical diagnosis with histologic confirmation), probable (typical clinical syndrome without histologic confirmation), or possible (atypical clinical features but no alternative diagnosis apparent; no histologic confirmation). Typical sensitivity and specificity values for the diagnosis of probable Alzheimer's disease with the use of these criteria are 0.65 and 0.75, respectively.⁷

The classic clinical features of Alzheimer's disease are an amnesic type of memory impairment,^{8,9} deterioration of language,¹⁰ and visuospatial deficits.^{11,12} Motor and sensory abnormalities, gait disturbances, and seizures are uncommon until the late phases of the disease.⁶

Functional and behavioral disturbances are characteristic of the disease. Patients progress from the loss of higher-level activities of daily living, such as check writing and the use of public transportation, through abnormalities of basic activities of daily living,

such as eating, grooming, and using the toilet, as the disease enters advanced phases.¹³ Behavioral disturbances also progress over the course of the illness.⁵ Mood change and apathy commonly develop early and continue for the duration of the disease. Psychosis and agitation are characteristic of the middle and later phases of the disease.¹⁴

As part of the assessment of dementia, laboratory studies are necessary to identify causes of dementia and coexisting conditions that are common in the elderly. Thyroid-function tests and measurement of the serum vitamin B₁₂ level are required to identify specific alternative causes of dementia. A complete blood count; measurement of blood urea nitrogen, serum electrolyte, and blood glucose levels; and liver-function tests should be performed.¹⁵ Specialized laboratory studies — such as a serologic test for syphilis, the erythrocyte sedimentation rate, a test for human immunodeficiency virus antibody, or screening for heavy metals — are indicated when historical features or clinical circumstances suggest that infections, inflammatory diseases, or

exposure to toxins may be contributing to the dementia.

Neuroimaging plays an important role in the diagnosis of Alzheimer's disease and is particularly helpful in excluding alternative causes of dementia. It is currently recommended that patients undergo structural imaging of the brain with computed tomography (CT) or magnetic resonance imaging (Fig. 1A) at least once in the course of their dementia.¹⁵ Functional imaging with positron-emission tomography (Fig. 1B) or single-photon-emission CT may be helpful in the differential diagnosis of disorders associated with dementia.¹⁶

The low rates of recognition of dementia by family members and physicians^{17,18} constitute a major barrier to appropriate care for many patients with Alzheimer's disease. (Rates of such "failure to recognize" are reportedly 97 percent for mild dementia and 50 percent for moderate dementia.) Patients with complex presentation or challenging management issues should be referred to a specialist with expertise in dementia.

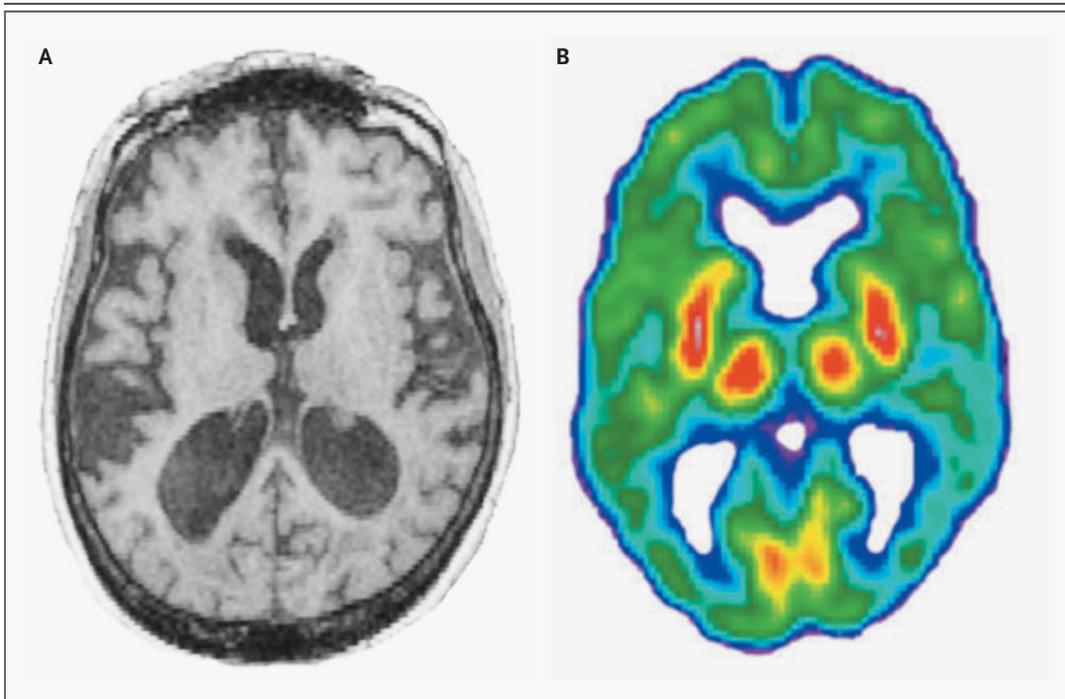


Figure 1. Scans of Patients with Probable Alzheimer's Disease.

In Panel A, a magnetic resonance image shows cortical atrophy and ventricular enlargement. In Panel B, a positron-emission tomographic scan shows reduced glucose metabolism in the parietal lobes bilaterally (blue-green) as compared with more normal metabolism in other cortical areas (yellow).

PATHOPHYSIOLOGY

There is increasing consensus that the production and accumulation of beta-amyloid ($A\beta$) peptide is central to the pathogenesis of Alzheimer's disease.¹⁹ Evidence supporting a pivotal role for $A\beta$ includes the following: mutations in the amyloid precursor protein lead to early-onset Alzheimer's disease; all currently known mutations associated with Alzheimer's disease increase the production of $A\beta$; in patients with trisomy 21 (Down's syndrome) and three copies of the gene for amyloid precursor protein, neuropathological characteristics of Alzheimer's disease develop by midlife; $A\beta$ is neurotoxic in vitro and leads to cell death; overexpression of human amyloid precursor protein in transgenic mouse models of Alzheimer's disease results in neuritic plaques similar to those seen in humans with Alzheimer's disease; transgenic mice overexpressing the human amyloid precursor protein have evidence of learning and memory deficits, in concert with the accumulation of amyloid; the apolipoprotein E $\epsilon 4$ genotype, a major risk factor for Alzheimer's disease, leads to accelerated deposition of amyloid; and the generation of anti-amyloid antibodies in humans with Alzheimer's disease seems to ameliorate the disease process.²⁰⁻²⁴ Formation of neurofibrillary tangles, oxidation and lipid peroxidation, glutamatergic excitotoxicity, inflammation, and activation of the cascade of apoptotic cell death are considered secondary consequences of the generation and deposition of $A\beta$ ¹⁹ (Fig. 2). This hypothesized amyloid cascade underlies attempts to modify the onset and course of Alzheimer's disease through identification of anti-amyloid agents, antioxidants, antiinflammatory drugs, compounds that limit the phosphorylation of tau protein, antiapoptotic agents, and glutamatergic N-methyl-D-aspartate-receptor antagonists.

Cell dysfunction and cell death in nuclear groups of neurons responsible for maintenance of specific transmitter systems lead to deficits in acetylcholine, norepinephrine, and serotonin.^{25,26} Alternate hypotheses regarding the pathophysiology of Alzheimer's disease place greater emphasis on the potential role of tau-protein abnormalities, heavy metals, vascular factors, or viral infections.

TREATMENT

ANTIAMYLOID THERAPIES

No anti-amyloid therapies are currently available. A program to vaccinate humans was implemented

after the observation that immunization with $A\beta$ reduces pathological signs of Alzheimer's disease in transgenic mice that have the amyloid precursor protein mutation.²⁷ This clinical trial was interrupted when encephalitis developed in 6 percent of the patients.²⁸ Post hoc analyses of a subgroup of 30 patients observed at a single site within the trial suggested that those patients who generated $A\beta$ antibodies had a reduction in disease progression.²⁴ Passive immunization represents an alternative and perhaps a safer vaccination strategy.²⁹

The enzymes responsible for liberating $A\beta$, a toxic fragment of 42 amino acids, from the amyloid precursor protein are β and γ secretases. Inhibitors of these enzymes are under active study.³⁰ The metabolism of cholesterol is intimately involved in the generation of $A\beta$, and preliminary evidence suggests that statins may be beneficial in reducing the accumulation of $A\beta$.³¹ Metal-binding compounds such as clioquinol may reduce oxidative injury associated with $A\beta$ and may inhibit the aggregation of the $A\beta$ peptide.³² High blood glucose levels may increase the levels of insulin and insulin-degrading enzymes,³³ redirecting the latter from an alternative role in the metabolism of $A\beta$. Some investigators suggest that analogues of insulin-degrading enzymes might represent therapeutic options. Strategies aimed at reducing the aggregation of $A\beta$ offer another therapeutic avenue to be explored.³⁴ The identification of valid targets and potential treatments suggests that disease-modifying therapies will emerge from this research arena.

NEUROPROTECTIVE APPROACHES

$A\beta$ protein seems to exert its neurotoxic effects through a variety of secondary mechanisms, including oxidative injury and lipid peroxidation of cell membranes, inflammation, hyperphosphorylation of tau protein, and increased glutamatergic excitotoxicity. Neuroprotective strategies have targeted these mechanisms in an effort to reduce the cell injury associated with the generation and aggregation of $A\beta$. Proof that these approaches are neuroprotective in humans is lacking; available data from animal models make this mechanism of activity most plausible.

ANTIOXIDANTS

The principal antioxidant strategy has involved treatment with alpha-tocopherol (vitamin E). A randomized, placebo-controlled trial compared the effect of vitamin E, selegiline, the two drugs together, and placebo in patients with Alzheimer's disease.³⁵

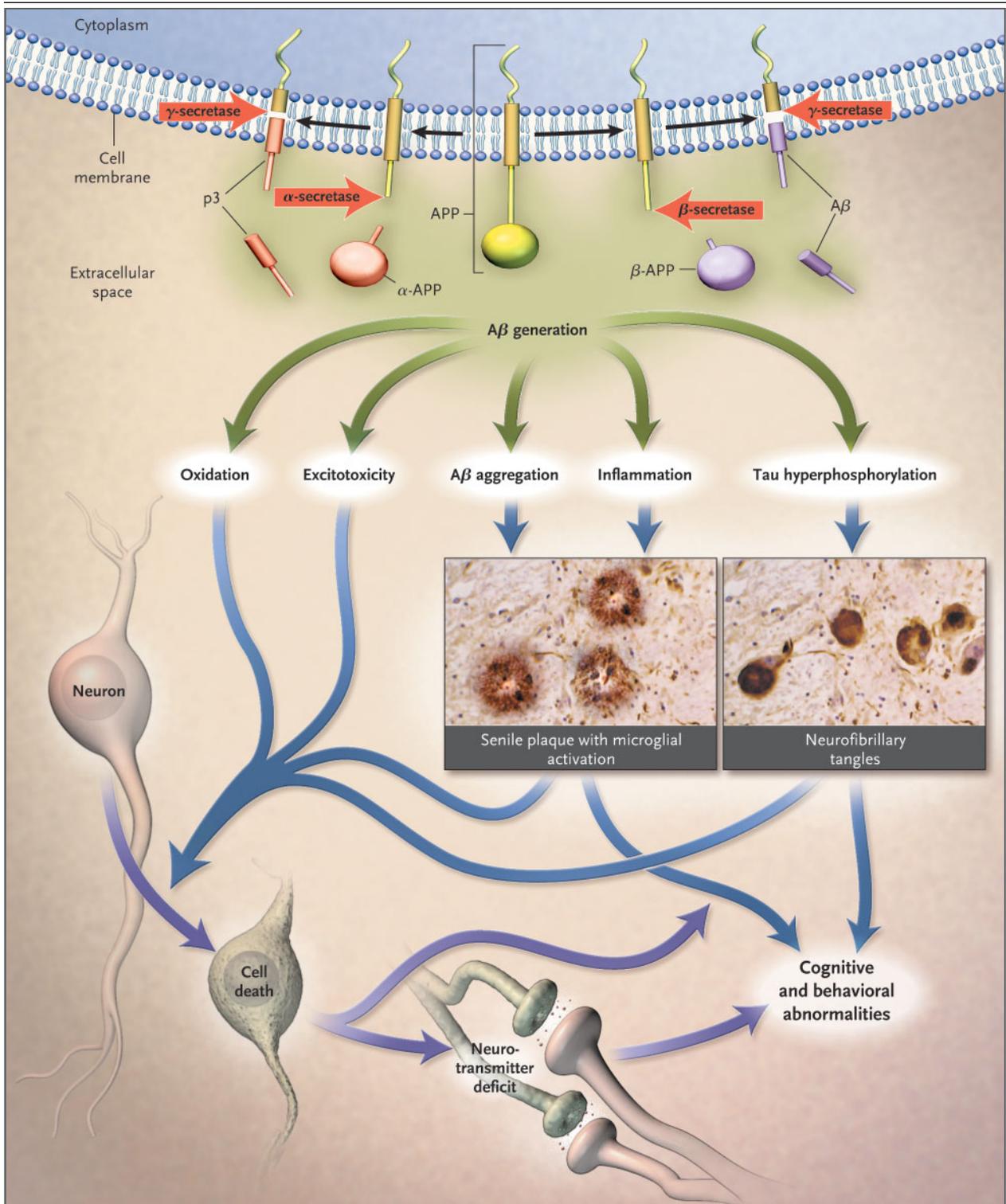


Figure 2. Putative Amyloid Cascade.

This hypothesis of the amyloid cascade, which progresses from the generation of the beta-amyloid peptide from the amyloid precursor protein, through multiple secondary steps, to cell death, forms the foundation for current and emerging options for the treatment of Alzheimer's disease. APP denotes amyloid precursor protein, and Aβ beta-amyloid.

The results of unadjusted comparisons showed no significant difference among the four groups in the study. However, when the severity of cognitive decline at baseline was included as a covariate, a significant delay in the primary outcomes (time to death, placement in a nursing home, development of severe dementia, or a defined severity of impairment of activities of daily living) was observed for patients in the selegiline, alpha-tocopherol, and combination-therapy groups, as compared with the placebo group. The increase in median time to one of the primary outcomes, as compared with the time in patients receiving placebo, was 230 days for patients receiving alpha-tocopherol, 215 days for those treated with selegiline, and 145 days for those receiving both agents. No differences in cognitive function were evident among the four groups. No statistically significant differences in vital signs, weight change, laboratory values, or 49 categories of adverse events emerged among the groups. On the basis of this study, many practitioners have added high-dose vitamin E supplements (2000 IU daily) to their standard treatment regimen for Alzheimer's disease. One retrospective study compared patients treated with a cholinesterase inhibitor plus vitamin E with historical controls and interpreted the results as indicating that the combination treatment is safe and beneficial.³⁶ Several but not all epidemiologic studies provide evidence supporting the concept that vitamin E, as well as vitamin C, has a role in delaying the onset of Alzheimer's disease.³⁷⁻³⁹

MEMANTINE

Memantine, an *N*-methyl-D-aspartate antagonist recently approved by the Food and Drug Administration (FDA) for the treatment of moderate-to-severe Alzheimer's disease, may interfere with glutamatergic excitotoxicity or may provide symptomatic improvement through effects on the function of hippocampal neurons.⁴⁰ A double-blind, placebo-controlled trial of memantine in patients with moderate-to-severe Alzheimer's disease showed the superiority of memantine over placebo as indicated by both the Activities of Daily Living Inventory and the Severe Impairment Battery (a neuropsychological test for patients with severe dementia), but not on the Global Deterioration Scale.⁴¹ Memantine was initiated at a dose of 5 mg daily. The dose was increased to 5 mg twice daily and then to 10 mg in the morning and 5 mg in the evening, until a final dose of 10 mg twice daily was reached (Table 1). There were no clinically relevant differences between patients in the memantine and placebo groups in terms of adverse events, laboratory values, electrocardiographic studies, or vital signs. When memantine was administered to patients with moderate-to-severe Alzheimer's disease who were receiving stable doses of a cholinesterase inhibitor, there was cognitive improvement, reduced decline in activities of daily living, and a reduced frequency of new behavioral symptoms as compared with those receiving placebo.⁴² The magnitude of the improvements in patients in these trials is modest, with improvement or temporary stabilization observed in daily function or behavior.

Table 1. Clinical Pharmacology of Agents Useful for Reducing the Signs of Dementia.*

Characteristic	Donepezil	Rivastigmine	Galantamine	Memantine
Time to maximal serum concentration (hr)	3–5	0.5–2	0.5–1	3–7
Absorption affected by food	No	Yes	Yes	No
Serum half-life (hr)	70–80	2†	5–7	60–80
Protein binding (%)	96	40	0–20	45
Metabolism	CYP2D6, CYP3A4	Nonhepatic	CYP2D6, CYP3A4	Nonhepatic
Dose (initial/maximal)	5 mg daily/ 10 mg daily	1.5 mg twice daily/ 6 mg twice daily	4 mg twice daily/ 12 mg twice daily	5 mg daily/ 10 mg twice daily
Mechanism of action	Cholinesterase inhibitor	Cholinesterase inhibitor	Cholinesterase inhibitor	NMDA-receptor antagonist

* CYP2D6 denotes cytochrome P-450 enzyme 2D6, CYP3A4 cytochrome P-450 enzyme 3A4, and NMDA *N*-methyl-D-aspartate.

† Rivastigmine is a pseudo-irreversible acetylcholinesterase inhibitor that has an eight-hour half-life for the inhibition of acetylcholinesterase in the brain.

ANTIINFLAMMATORY AGENTS

The brains of patients with Alzheimer's disease have microscopic evidence of inflammation,⁴³ an observation that led to a series of clinical trials with steroidal or nonsteroidal antiinflammatory drugs. Negative outcomes (no benefit as compared with placebo) have been reported for trials of prednisone,⁴⁴ diclofenac,⁴⁵ rofecoxib (a selective cyclooxygenase-2 inhibitor), and naproxen (a mixed cyclooxygenase-1 and cyclooxygenase-2 inhibitor).⁴⁶ Thus, evidence is insufficient to support treatment with antiinflammatory agents for patients with Alzheimer's disease. Primary-prevention trials have not yet explored the possible value of these agents in preventing Alzheimer's disease.

HORMONE-REPLACEMENT THERAPY

Epidemiologic observations suggested that estrogen-replacement therapy might reduce the occurrence of Alzheimer's disease in postmenopausal women, but randomized, placebo-controlled trials of estrogen-replacement therapy in such women showed no benefit.^{47,48} The Women's Health Initiative study of estrogen plus medroxyprogesterone acetate showed an increased risk of dementia among postmenopausal women who lacked cognitive deficits at the time of randomization and were assigned to the active-treatment group.⁴⁹ Thus, hormone-replacement therapy is not recommended for treatment or prevention of Alzheimer's disease.

CHOLINESTERASE INHIBITORS

Cholinesterase inhibitors are approved for the treatment of mild-to-moderate Alzheimer's disease and should be considered as a standard of care for patients with Alzheimer's disease.^{50,51} Four cholinesterase inhibitors are available: tacrine, donepezil, rivastigmine, and galantamine. Of these, tacrine is now rarely used, since it has hepatotoxic effects⁵² in approximately 40 percent of those exposed; second-generation cholinesterase inhibitors seem less toxic, and their duration of action permits more convenient dosage regimens.

The pharmacologic characteristics of the three commonly used cholinesterase inhibitors are shown in Table 1. Donepezil is initiated at a dose of 5 mg per day, and the dose is increased to 10 mg per day after one month. The dose of rivastigmine increases from 1.5 mg twice daily to 3 mg twice daily, then to 4.5 mg twice daily, and to a maximal

dose of 6 mg twice daily. The dose may be increased at intervals of one to four weeks; fewer side effects emerge with longer periods between increases. Galantamine is initiated at a dose of 4 mg twice daily. The dose is increased first to 8 mg twice a day and finally to 12 mg twice daily. As with rivastigmine, longer periods between dosage increases are associated with a lower frequency of side effects.⁵³ Daily treatment with donepezil is effective in the dose range of 5 to 10 mg; rivastigmine, in the range of 6 to 12 mg; and galantamine, in the range of 16 to 24 mg.

For a drug to be approved by the FDA as an anti-dementia drug, two well-designed, clinically relevant trials (called pivotal trials) must demonstrate a significant difference between patients receiving the drug and patients receiving a placebo in terms of the scores for cognitive function and global assessment scales.⁵⁴ The cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-Cog)⁵⁵ is commonly used to establish efficacy with respect to cognitive function, and the Clinician Interview-Based Impression of Change scale with caregiver input (CIBIC-Plus)⁵⁶ is the global instrument most often used in clinical trials. When evaluated according to these measures, the three widely used cholinesterase inhibitors have similar efficacy.

Pivotal clinical trials have shown changes on the ADAS-Cog of 2.5 to 3.5 points (range of scores, 0 to 70, with higher scores indicating greater cognitive decline) and differences on the CIBIC-Plus of 0.3 to 0.5 (range of scores, 1 to 7, with a score of 1 indicating substantial improvement and 7 indicating marked deterioration) in patients receiving the drug as compared with patients receiving placebo.⁵⁷⁻⁵⁹ The ADAS-Cog shows a typical rate of increase of seven points annually in untreated populations.⁶⁰ A four-point decrease in the ADAS-Cog in the course of a clinical trial is equivalent to reversing the symptoms of the disease by approximately six months, and a seven-point decrement is equivalent to reversing the symptoms by approximately one year.

With some variability across studies, approximately twice as many patients who received an active cholinesterase inhibitor had a four-point improvement on the ADAS-Cog as patients receiving placebo (25 to 50 percent vs. 15 to 25 percent), and approximately three times as many patients receiving an active cholinesterase inhibitor had a seven-point improvement (12 to 20 percent, vs. 2 to 6 percent among those taking placebo).⁵³ Studies of the re-

sponses suggest that more patients had less decline than had a measurable improvement in symptoms.

Secondary measures included in clinical trials suggest that cholinesterase inhibitors may help affected patients maintain their ability to perform activities of daily living, have fewer behavioral changes, be less of a burden to the caregiver, and defer their placement in nursing homes.⁵³ However, most of the trials were not randomized to ensure baseline equivalence among these features. Thus, a beneficial effect remains to be firmly established. Some studies also suggest that cholinesterase inhibitors may improve the cognition of patients in more advanced phases of Alzheimer's disease, but further studies are needed.⁶¹ Thus, cholinesterase inhibitors may slow cognitive decline or functional deterioration temporarily, or they may reduce the emergence of new behavioral disturbances.

Side effects reported in clinical trials of cholinesterase inhibitors included nausea, vomiting, and diarrhea, as well as weight loss, insomnia, abnormal dreams, muscle cramps, bradycardia, syncope, and fatigue. In pivotal trials, nausea occurred in 17 percent of patients receiving donepezil, 48 percent of patients receiving rivastigmine, and 37 percent of patients receiving galantamine; vomiting in 10 percent, 27 percent, and 21 percent, respectively; and diarrhea in 17 percent, 19 percent, and 12 percent, respectively.⁵⁷⁻⁵⁹ These percentages reflect the occurrence of adverse effects during the initiation of treatment; the frequency of adverse events is reduced with slower rates of drug titration and is generally lower during maintenance therapy.⁵³ Only a small number of subjects withdrew from a trial because of side effects. Clinical experience suggests that introducing cholinesterase inhibitors at low doses, increasing the dose gradually, and administering the medication with meals may limit gastrointestinal side effects. Few drug interactions have been reported with cholinesterase inhibitors.

The optimal duration of treatment with cholinesterase inhibitors is uncertain. The duration of most blinded trials has been six months. Trials lasting one year have also shown a difference between patients receiving the active drug and patients receiving a placebo.⁶² Studies in which the rate of deterioration in the placebo group was extrapolated and compared with the level of function of patients continuing treatment with a cholinesterase inhibitor suggest that patients continue to derive benefit from therapy for two to three years.⁶³

Whether some patients respond to one agent

better than another has not been established. Indications for switching from one cholinesterase inhibitor to another include allergic responses, unmanageable side effects, the preferences of the family, and unmitigated cognitive decline after a treatment trial lasting at least six months.⁵³ Specific strategies for switching agents have not been tested in adequate numbers of patients, though it is thought that interruption of therapy for a month or more might be detrimental. Patients who took donepezil after a three-week washout period, during which they received placebo, attained higher levels of function than patients who underwent a six-week washout period with placebo.⁶⁴ Concurrent administration of more than one cholinesterase inhibitor has not been studied and is not advised. Cholinesterase inhibitors are commonly administered with vitamin E and memantine.⁴²

OTHER TREATMENTS FOR COGNITIVE DETERIORATION

A variety of agents have been tested for their potential value in the treatment of cognitive deterioration in Alzheimer's disease. In 2001, the Quality Standards Subcommittee of the American Academy of Neurology reviewed 48 medications that had been tested for their effect on cognitive function and decided that there were insufficient data to permit assessment and recommendations with respect to agents other than cholinesterase inhibitors and vitamin E.⁵⁰

Herbal supplements and so-called nutraceuticals are commonly used by patients for the treatment of Alzheimer's disease and by family members as a putative preventive strategy. In some trials, but not all, ginkgo biloba had small but statistically significant effects as compared with placebo in patients with Alzheimer's disease.⁶⁵ A primary-prevention trial to determine whether ginkgo biloba reduces the rate of development of Alzheimer's disease is currently in progress. Huperzine A is a cholinesterase inhibitor, and preliminary clinical trials have shown it to be of benefit in Alzheimer's disease.⁶⁶

MANAGEMENT OF NEUROPSYCHIATRIC SYMPTOMS AND BEHAVIORAL DISTURBANCES

Neuropsychiatric symptoms, known to be very common among patients with Alzheimer's disease, have been reported in more than 80 percent of subjects in most studies.¹⁴ When behavioral abnormalities develop in a patient, they should be managed nonphar-

macologically first, before pharmacologic agents, with their attendant risk of adverse events and additional expense, are administered.⁶⁷ A wide variety of nonpharmacologic interventions have been studied, most often in nursing homes and long-term care facilities, for the treatment of behavioral disturbances in Alzheimer's disease.^{50,67,68} Such interventions have included music, videotapes of family members, audiotapes of the voices of caregivers, walking and light exercise, and sensory stimulation and relaxation. Little consideration has been given to nonpharmacologic interventions for patients living in the community, but attention has been given to interventions that may benefit the caregivers of these patients. Given the relatively benign nature of nonpharmacologic interventions, it would be practical to explore these techniques when treating behavior disturbances that are associated with Alzheimer's disease.⁵⁰

Few randomized, controlled trials have addressed the optimal psychopharmacologic agents for the treatment of behavioral changes in patients with Alzheimer's disease. Recommendations are made on the basis of small trials, open-label studies, and extrapolation from studies of patients without dementia (Table 2).

Atypical antipsychotic agents are the preferred medications for the management of psychosis or agitation (with or without psychosis). They produce fewer side effects such as parkinsonism and tardive dyskinesia than do conventional neuroleptic drugs. Double-blind, controlled trials support the efficacy of risperidone and olanzapine in reducing the rate of psychosis and agitation in patients with Alzheimer's disease.⁶⁹⁻⁷² Active comparison trials and double-blind, placebo-controlled trials have shown that haloperidol, a neuroleptic antipsychotic agent, also reduces agitation.^{73,74} A meta-analysis of controlled trials of neuroleptic agents showed that approximately 20 percent more patients respond to active therapy than to placebo for the treatment of dementia. Greater treatment responses were observed with typical and atypical antipsychotic agents than with placebo. Current evidence favors atypical antipsychotic agents for the treatment of patients with psychosis or agitation. Patients with inadequate responses may benefit from therapy with mood stabilizers or antidepressants alone or in combination with antipsychotic agents.

Mood-stabilizing agents may reduce behavioral disturbances in patients with Alzheimer's disease. Agitation appeared to improve significantly in trials

with carbamazepine.⁷⁵ Divalproex sodium has been studied for its effects on agitation, with mixed results.^{76,77}

Several clinical trials have addressed the treatment of depression in patients with Alzheimer's disease. The number of placebo-controlled studies that showed no effect from the use of antidepressants was almost equal to the number that showed a benefit. Selective serotonin-reuptake inhibitors and tricyclic antidepressants have been included in both negative and positive trials. Studies involving severely depressed patients and a rigorous study design tended to show positive effects. Combined serotonin- and noradrenergic-reuptake inhibitors are commonly used in elderly patients; tricyclic antidepressants have anticholinergic side effects and are used less often. Most clinicians choose selective serotonin-reuptake inhibitors when treating depression in patients with Alzheimer's disease.⁷⁸⁻⁸⁰

Few psychopharmacologic agents have been approved specifically for use in patients with dementia or Alzheimer's disease. Nearly all prescriptions for these drugs are for off-label uses and represent extrapolation from observations of the effects of these agents in patients without dementia. However, because efficacy and side effects in patients with Alzheimer's disease may be different from those in patients without dementia, additional studies are needed.

HEALTH MAINTENANCE AND GENERAL MEDICAL TREATMENT

As Alzheimer's disease progresses, various conditions develop that may lead to death, such as septicemia, pneumonia and upper respiratory infections, nutritional disorders, pressure sores, fractures, and wounds.⁸¹ Management of these conditions is critical. In the early stages of Alzheimer's disease, the clinician should encourage health maintenance activities, including exercise, the control of hypertension and other medical conditions, annual immunization against influenza, dental hygiene, and the use of eyeglasses and hearing aids as needed for visual and auditory impairments.⁸² In later phases of the disease, it is important to address basic requirements such as nutrition, hydration, and skin care. Decisions about the use of methods of extending life, such as gastrostomy, intravenous hydration, and the administration of antibiotics, should respect advance directives by patients and incorporate guidance from surrogate decision makers.

Table 2. Psychotropic Agents Useful for the Treatment of Neuropsychiatric Symptoms and Behavioral Disturbances in Patients with Alzheimer's Disease.

Type and Drug	Initial Daily Dose	Final Daily Dose (Range)	Targeted Symptoms
Atypical antipsychotic			Psychosis and agitation
Risperidone	0.5 mg daily	1.0 mg (0.75–1.5 mg daily)	
Olanzapine	2.5 mg daily	5.0 mg (5–10 mg daily)	
Quetiapine	25 mg daily	200 mg (50–150 mg twice daily)	
Ziprasidone	20 mg daily	40 mg (20–80 mg twice a day)	
Aripiprazole	10 mg daily	10 mg (10–30 mg daily)	
Neuroleptic			Psychosis and agitation
Haloperidol	0.25 mg daily	2 mg (1–3 mg daily)	
Mood stabilizer			Agitation
Divalproex sodium	125 mg twice a day	500 mg (250–500 mg twice a day)	
Carbamazepine	200 mg twice a day	400 mg (200–500 mg twice a day)	
Selective serotonin-reuptake inhibitor			Depression, anxiety, psychosis, and agitation
Citalopram	10 mg daily	20 mg (20–40 mg daily)	
Escitalopram	5 mg daily	10 mg (10–20 mg daily)	
Paroxetine	10 mg daily	20 mg (10–40 mg daily)	
Sertraline	25 mg daily	75 mg (75–100 mg daily)	
Fluoxetine	5 mg daily	10 mg (10–40 mg daily)	
Tricyclic antidepressant			Depression
Nortriptyline	10 mg daily	50 mg (25–100 mg daily)	
Desipramine	10 mg daily	100 mg (50–200 mg daily)	
Serotonin- and noradrenergic-reuptake inhibitor			Depression and anxiety
Venlafaxine	25 mg twice a day	200 mg (100–150 mg twice a day)	
Noradrenergic and specific serotonergic antidepressant			Depression
Mirtazapine	7.5 mg daily	15 mg (15–30 mg daily)	

ALLIANCE WITH CAREGIVERS

An alliance between the clinician and the caregiver is essential in treating patients with Alzheimer's disease. Caregivers are responsible for supervising patients who live in the community and frequently continue to visit and provide assistance after a patient has been institutionalized. Caregivers are also responsible for administering medication, implementing nonpharmacologic treatment, and promoting the patient's general health and well-being and a meaningful quality of life. Caregivers must make decisions regarding driving, advance directives, financial management, removal of firearms, home safety, and programs such as Safe Return, a nationwide network created by the Alzheimer's Association.⁸³

Studies show that caregivers of patients with Alzheimer's disease rate their own health as relatively poor. Furthermore, they endure a greater number of illnesses, have more somatic symptoms, have more depression and anxiety, use more health care, and engage in fewer preventive-health activities than

people who are not caregivers.⁸⁴ Self-help groups, support groups, education, skills training, counseling, and psychotherapy may help caregivers. Most of these interventions have been associated with reduced psychological distress and improved knowledge on the part of caregivers, yet they have failed to reduce the caregiver's burden.^{85,86} Referring caregivers to a family-assistance organization is an important element of their care.^{83,87,88}

CONCLUSIONS

Current therapies for patients with Alzheimer's disease may ease symptoms by providing temporary improvement and reducing the rate of cognitive decline. Given the wide array of available molecular targets and the rapid progress toward identifying potential therapeutic compounds, the development of interventions that substantially delay the onset or modify the progression of Alzheimer's disease can be anticipated.

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