

Review Article

*Drug Therapy*ALASTAIR J.J. WOOD, M.D., *Editor*

TREATMENT OF ALZHEIMER'S DISEASE

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ALZHEIMER'S disease, which is characterized by progressive loss of memory and cognitive function, affects 15 million people worldwide. The incidence increases steadily from 0.5 percent per year at the age of 65 years to nearly 8 percent per year after the age of 85 years.¹ Because survival for a decade is common, the prevalence increases from 3 percent at the age of 65 years to 47 percent after the age of 85 years.² Mutations in the gene for the amyloid precursor protein and the genes for presenilin 1 and 2 cause rare, dominantly inherited forms of the disease occurring before the age of 60 years, and the $\epsilon 4$ variant of apolipoprotein E is associated with the sporadic form and some familial forms with onset after the age of 60 years.^{3,4}

Criteria for the diagnosis of Alzheimer's disease were established in 1984 (Table 1).⁵ Patients who meet the criteria and who have no other illness that can cause dementia, such as hypothyroidism or cerebrovascular disease, receive a diagnosis of probable Alzheimer's disease. If they meet the criteria and also have another disease that can cause dementia, they are given a diagnosis of possible Alzheimer's disease. Definite cases are those confirmed by the postmortem findings of dense plaques containing the β -amyloid peptide and elements of degenerating neurons, neurofibrillary tangles composed of abnormally phosphorylated tau protein, and loss of neurons and synapses in the brain. Degeneration in the basal forebrain profoundly reduces the content of acetylcholine and the activities of choline acetyltransferase.⁶ Although other neurotransmitters can be involved, the loss of acetylcholine occurs early and correlates with the impairment

of memory.^{7,8} Symptomatic treatment for Alzheimer's disease has focused on augmenting cholinergic neurotransmission.⁸

METHODOLOGIC CONSIDERATIONS

This review is limited to drugs approved by the Food and Drug Administration (FDA) specifically for Alzheimer's disease, drugs approved for other conditions but used in patients with Alzheimer's disease, and drugs under consideration for approval. Only drugs given in clinical trials for at least six months are reviewed in detail.

The goals of treatment in patients with Alzheimer's disease have been to improve or at least slow the loss of memory and cognition and to maintain independent function. The FDA recommended that all clinical trials whose results are to be submitted with new-drug applications for Alzheimer's disease use the Alzheimer's Disease Assessment Scale, Cognitive Subscale, as the primary outcome measure.⁹⁻¹¹ This subscale is an 11-item assessment of memory, orientation, attention, reasoning, language, and motor performance.¹¹ Scores on this subscale range from 0 (indicating no impairment) to 70 (severe impairment) (Table 2). Scores may decrease (i.e., improve) over time in healthy elderly subjects as a result of a learning effect. The average score on the cognitive subscale of the Alzheimer's Disease Assessment Scale increases (i.e., worsens) by 4 to 5 percent in a six-month period (8 to 10 percent annually) in untreated patients with Alzheimer's disease.¹⁵ For a drug to be considered effective, the scores of the persons receiving the drug should decrease significantly more than the scores for persons receiving placebo.

Differences in the score on the cognitive subscale of the Alzheimer's Disease Assessment Scale may not always be clinically obvious. Rating scales based on the clinician's assessment, such as the Clinician Interview-Based Impression of Change scale¹³ and the Clinical Global Impression of Change scale,¹² have also been recommended. These seven-point ordinal scales allow physicians to rate changes from 1 (marked improvement) to 7 (marked worsening) (Table 2). Over a period of six months, the increase in the scores on these scales is less than 1 percent of the total range of the scale for healthy elderly people^{13,16} and from 2 to 11 percent for people with Alzheimer's disease. Although these clinician-based ratings correlate well with scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale, they are considered "independent, multidimensional assessments of cognitive, behavioral and functional change."¹² In this review we express study results as the percent

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TABLE 1. CRITERIA FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE.*

DIAGNOSIS	CRITERIA
Probable Alzheimer's disease	All of the following must be present: Dementia established by examination and documented by objective testing Impairment in memory and at least one other cognitive function (e.g., language or perception) Progressive worsening of memory and at least one other cognitive function No disturbance in consciousness Onset between 40 and 90 years of age Absence of another brain disorder or systemic disease that might cause dementia In addition, the diagnosis may be supported by one or more of the following: Loss of motor skills Diminished independence in activities of daily living and altered patterns of behavior Family history of similar disorder Laboratory results consistent with the diagnosis (e.g., cerebral atrophy on computed tomography)
Possible Alzheimer's disease	Fulfillment of the above criteria with variation in the onset of symptoms or manifestations or in clinical course; or a single, but gradually progressive, cognitive impairment without an identifiable cause Another brain disorder or systemic disease that is sufficient to produce dementia, but that is not considered to be the underlying cause of the dementia in the patient
Definite Alzheimer's disease	Fulfillment of the above clinical criteria and histologic evidence of Alzheimer's disease based on examination of brain tissue obtained at biopsy or autopsy

*Criteria were adapted from McKhann et al.⁵

TABLE 2. TESTS USED AS OUTCOME MEASURES IN CLINICAL TRIALS OF TREATMENTS FOR ALZHEIMER'S DISEASE.

TEST	RANGE OF SCORES*	DESCRIPTION	PURPOSE
Alzheimer's Disease Assessment Scale, Cognitive Subscale ¹¹	0 (no impairment) to 70 (severe impairment) Annual decline, 8–10% 6-mo decline, 4–5%	Standardized assessment of cognitive domains: recall naming, language, orientation, construction, praxis, recognition	Used as a primary outcome measure to assess effect on cognitive performance
Clinical Global Impression of Change scale ¹²	1 (marked improvement) to 7 (marked worsening) Annual decline, 19% 6-mo decline, 11%	Organized but unstructured method of clinically assessing observable change by interview with patient, informants, and care givers	Used as a primary outcome measure to assess clinically relevant change
Clinician Interview-Based Impression of Change scale ¹³	1 (marked improvement) to 7 (marked worsening) Annual decline, unavailable 6-mo decline, 1.4%†	Nonstructured scale for assessing clinical change. Clinician Interview-Based Impression of Change Plus includes information from informant and care giver	Used as a primary outcome measure to assess clinically relevant change
Mini-Mental State Examination ¹⁴	0 (severe impairment) to 30 (no impairment) Annual decline, 10% 6-mo decline, 5%	Standardized mental-status examination assessing orientation and briefly assessing memory and other cognitive skills	Used to identify a range of cognitive deficit for study enrollment and as a secondary outcome measure

*Decline indicates a decline in performance. Percentages indicate the difference in the score as a percentage of the total range of scores for the scale in question.

†Data are from Knopman et al.¹³ Percent change is reported for the Clinician Interview-Based Impression of Change (without information from an informant), which may reduce the observed decline in function.

changes in the treated group corrected for any changes in the placebo group.

CHOLINERGIC AUGMENTATION THERAPY

Precursors of acetylcholine, such as lecithin and choline, are ineffective in Alzheimer's disease^{17–19} because they do not increase central cholinergic activity.

Postsynaptic cholinergic receptor agonists have had unacceptable adverse effects.^{20–23} The results with cholinesterase inhibitors (anticholinesterases) have been encouraging, because they increase cholinergic synaptic transmission by inhibiting acetylcholinesterase in the synaptic cleft, thereby decreasing the hydrolysis of acetylcholine released from presynaptic neurons. Drugs in this class differ from one another in the way

TABLE 3. CLINICAL TRIALS OF CHOLINESTERASE INHIBITORS IN PATIENTS WITH ALZHEIMER'S DISEASE.*

DRUG	STUDY	DURATION OF STUDY (WK)	DAILY DOSE	CHANGE IN ALZHEIMER'S DISEASE ASSESSMENT SCALE, COGNITIVE SUBSCALE, WITH TREATMENT (%)†	CHANGE IN CLINICAL GLOBAL MEASURES WITH TREATMENT (%)‡	ADVERSE-EVENT-RELATED DROPOUTS (%)		MOST COMMON ADVERSE EVENTS (%)		
						DRUG	PLACEBO	EVENT	DRUG	PLACEBO
Controlled-release physostigmine	Thal et al. ²⁶	24	36 mg (2 divided doses)	4.1	3.7	57	9	Nausea	79	17
								Vomiting	57	8
								Dizziness	30	13
Tacrine	Knapp et al. ²⁷	30	160 mg (4 divided doses)	5.9	5.7	55§	11	Elevated serum aminotransferase concentrations	29	<11
								Nausea and vomiting	28	<11
Donepezil	Rogers et al. ²⁸	24	10 mg	4.1	6.3	16	7	Nausea	17	4
								Diarrhea	17	7
								Vomiting	10	2
Metrifonate	Morris et al. ²⁹	26	60–80 mg	4.1	4.0	8	4	Diarrhea	18	8
								Leg cramps	9	<1
Rivastigmine	Rösler et al. ³⁰	26	6–12 mg (2 divided doses)	5.4	4.1	29	15	Nausea	35	11
								Vomiting	27	3
Eptastigmine	Imbimbo et al. ³¹	24	60 mg (3 divided doses)	3.3	4.7	8	7	Anxiety	8	7
								Granulocytopenia	6	2
								Bradycardia	3	1
								Abdominal pain	3	2

*Results are for the maximal doses in the longest reported clinical trials using intention-to-treat analyses.

†The change in the score on the scales is calculated as the percent change in the treated group corrected for any change in the placebo group.

‡The percentages for the clinical global measures (the Clinician Interview-Based Impression of Change scale or the Clinical Global Impression of Change scale) are based on a seven-point scale.^{12,13}

§The reported rate is for all doses, including lower ones.

they inhibit acetylcholinesterase activity.²⁴ Reversible inhibitors, such as tacrine and donepezil, bind to acetylcholinesterase, inhibiting formation of the enzyme–acetylcholine complex.²⁵ “Pseudoirreversible” inhibitors, such as rivastigmine, do not directly inhibit the formation of the enzyme–acetylcholine complex but decrease enzyme activity directly. The duration of action of these drugs depends not only on the type of inhibition produced, but also on the rate of enzyme resynthesis. Anticholinesterases also differ in selectivity for different cholinesterases. Tacrine and physostigmine inhibit both acetylcholinesterase and butyrylcholinesterase, whereas donepezil and rivastigmine are selective inhibitors of acetylcholinesterase.²⁴ Although several anticholinesterases are available (Table 3), they have not been directly compared.

Physostigmine

Physostigmine, a tertiary amine, is a nonselective reversible inhibitor of acetylcholinesterase and butyrylcholinesterase. In initial trials of physostigmine, administration every 2 hours was required, because of its 30-minute plasma half-life.^{32–35} In a six-week multicenter trial in 1111 patients, a controlled-release formulation given twice daily decreased scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale 2.4 percent (as described above).³⁶ Similar

changes were noted on the Clinical Global Impression of Change scale. In a 24-week multicenter trial of two different doses of controlled-release physostigmine, 36 mg daily resulted in a 4.1 percent decrease in the score on the cognitive subscale of the Alzheimer's Disease Assessment Scale and a similar degree of improvement on the clinical rating scales.²⁶ Seventy-nine percent of the patients treated with active drug reported nausea, 57 percent reported vomiting, 30 percent reported dizziness, 26 percent reported diarrhea, and 10 to 19 percent reported anorexia, dyspepsia, or abdominal discomfort (Table 3). The majority of patients in the two trials did not complete the study.^{26,36} Physostigmine has not been approved by the FDA for the treatment of Alzheimer's disease.

Tacrine

Tacrine (tetrahydroaminoacridine) is a nonselective, reversible anticholinesterase that was approved for use in Alzheimer's disease in 1993. Its plasma half-life is two to four hours, and therefore it must be given four times daily. Absorption decreases with food intake. There have been several brief studies of tacrine.³⁷ In a 30-week study of 663 patients, those randomly assigned to receive 160 mg of tacrine per day had a 5.9 percent decrease in the score on the cognitive subscale of the Alzheimer's Disease Assessment

Scale (Table 3).²⁷ Fifty-five percent of the tacrine-treated patients dropped out of the study because of adverse effects. Among those who were able to continue taking tacrine, fewer entered nursing homes or died (3 percent and 4 percent, respectively) than among those who took lower doses (7 percent for both).³⁸ Tacrine use has been limited because it causes asymptomatic elevation of serum aminotransferase concentrations.^{37,39} Among 12,000 patients, 29 percent had high serum aminotransferase values, 28 percent had nausea and vomiting, 14 percent had diarrhea, 9 percent had dyspepsia or anorexia, and 7.5 percent had myalgia. Few patients are treated with tacrine today.³⁹

Donepezil

Donepezil is a reversible, selective anticholinesterase that was approved for use in Alzheimer's disease in 1996. As compared with tacrine and physostigmine, donepezil has minimal peripheral anticholinesterase activity and a longer plasma half-life, allowing for once-daily administration.^{40,41} Two 24-week clinical trials of donepezil including a total of 1291 patients with Alzheimer's disease who received either 5 mg or 10 mg of donepezil per day resulted in up to a 4.1 percent decrease in the score on the cognitive subscale of the Alzheimer's Disease Assessment Scale and a 6.3 percent decrease in the score on the Clinician's Interview-Based Impression of Change scale (Table 3).^{28,42} Approximately 80 percent of patients receiving either dose of donepezil completed the studies. The most frequent adverse effects were nausea, diarrhea, and vomiting; insomnia occurred in up to 14 percent. The once-a-day regimen and the drug's reasonable tolerability and efficacy have made donepezil widely used in patients with Alzheimer's disease.

Metrifonate

Metrifonate (trichlorfon), an anthelmintic drug with no anticholinesterase activity, undergoes nonenzymatic hydrolysis to dichlorvos, a pseudoirreversible inhibitor of anticholinesterase.⁴³ Its plasma half-life is longer than that of physostigmine or donepezil, and it rapidly enters the brain.^{43,44} In two 12-week clinical trials in 530 patients, there was a 4 percent decrease in the score on the cognitive subscale of the Alzheimer's Disease Assessment Scale and the Clinician Interview-Based Impression of Change scale in patients treated with metrifonate.^{45,46} In a 26-week trial in 408 patients given a higher dose, the improvement was similar.²⁹ The most common adverse effects were diarrhea (18 to 19 percent of patients) and leg cramps (9 percent). Leg cramps and muscle weakness have occurred in phase 3 trials of this drug.

Rivastigmine

Rivastigmine is a relatively selective pseudoirreversible inhibitor of acetylcholinesterase with a 10-hour duration of action.^{47,48} Two 26-week multicenter tri-

als in a total of 1424 patients with Alzheimer's disease who were randomly assigned to receive either a low dose (1 to 4 mg) or a high dose (6 to 12 mg) of rivastigmine or placebo have been reported.^{30,49} In one trial, scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale were better by 5.4 percent with the high dose,⁴⁹ but 35 percent of the patients had nausea. Other adverse effects were vomiting, diarrhea, and anorexia. Six percent of patients in the low-dose group and 21 percent of patients in the high-dose group had a 7 percent or greater decrease in body weight; only 2 percent of the patients in the placebo group lost weight.⁴⁹ Similar results were reported for a European study (Table 3).³⁰ In these trials 29 to 43 percent of the high-dose group and 7 to 15 percent of the low-dose group withdrew because of adverse effects; 13 to 15 percent of the placebo group withdrew. Rivastigmine is approved for use in Europe.

Eptastigmine

Eptastigmine is a carbamate derivative of physostigmine and a reversible inhibitor of anticholinesterase.²⁴ In two 24-week trials, over 700 patients were randomly assigned to receive either a low dose (45 mg daily) or a high dose (60 mg daily) of eptastigmine or placebo.^{31,50} The patients given 45 mg or 60 mg of eptastigmine had a 3 percent reduction in the score on the cognitive subscale of the Alzheimer's Disease Assessment Scale and a 5 percent reduction in the score on the Clinician Interview-Based Impression of Change scale (Table 3).³¹ Gastrointestinal adverse effects were similar in frequency in the eptastigmine and placebo groups, as was the frequency of discontinuation. Sinus bradycardia was more frequent in the eptastigmine group. A dose-dependent transient granulocytopenia occurred in 6 percent of the high-dose group, as compared with 2 percent in the low-dose and placebo groups.³¹ The adverse hematologic effects reported in these two studies^{31,50} have resulted in the suspension of further clinical trials.²⁴

Efficacy of Cholinesterase-Inhibitor Drugs

Tacrine and donepezil, the only drugs approved for Alzheimer's disease in the United States, must be viewed as palliative treatments. They result in small but measurable benefits in terms of cognitive-test results as compared with placebo or no treatment. Although there are no differences in the benefits of the different cholinesterase inhibitors, the adverse effects associated with the drugs vary considerably. At maximal doses, tacrine and donepezil have similar benefits over placebo, but donepezil has fewer side effects and can be given once a day.

Treatment with cholinesterase inhibitors can begin at any time after diagnosis, because their efficacy, though limited, is established for patients with mild or moderate disease. There is insufficient information

TABLE 4. DRUGS USED TO SLOW OR DELAY THE PROGRESSION OF ALZHEIMER'S DISEASE.

DRUG	STUDY	DURATION OF STUDY	TOTAL DAILY DOSE	OUTCOME MEASURE (REPORTED AS BENEFIT OVER PLACEBO)*	MOST COMMON ADVERSE EVENTS (%)		
					EVENT	DRUG	PLACEBO
Alpha-tocopherol	Sano et al. ^{56†}	2 yr	2000 IU	6-mo delay in disease progression	Falls	14	5
				No difference in Alzheimer's Disease Assessment Scale, Cognitive Subscale	Syncopal	7	4
Selegiline	Sano et al. ^{56†}	2 yr	10 mg	4-mo delay in disease progression	Falls	9	5
				No difference in Alzheimer's Disease Assessment Scale, Cognitive Subscale	Syncopal	10	4
Idebenone	Weyer et al. ⁵⁷	6 mo	270 mg	2.8% decrease in Alzheimer's Disease Assessment Scale, Cognitive Subscale	Elevated hepatic enzyme concentrations	4	Frequency not reported
				No difference in clinical global measures	Nausea	4	
Propentofylline	Marcusson et al. ⁵⁸	6 mo to 1 yr	900 mg	2% to 3% decrease in Short Syndrome Test‡	Nausea	10	4
				No difference in clinical global measures	Dizziness	9	4
					Headache	7	3
<i>Ginkgo biloba</i>	Le Bars et al. ⁵⁹	1 yr	120 mg	2.4% decrease in Alzheimer's Disease Assessment Scale, Cognitive Subscale	Gastrointestinal symptoms (frequency not reported)		
Acetyl-L-carnitine	Thal et al. ⁶⁰	1 yr	3 g	No difference in Alzheimer's Disease Assessment Scale, Cognitive Subscale	Body odor, increased appetite, rash (more common in drug than placebo group, but frequency not reported)		
				No difference in clinical global measures			

*Percentages indicate the percent changes in the treated group corrected for any changes in the placebo group.

†Disease progression in this study was measured by the time until death, nursing home placement, loss of ability to perform activities of daily living, or severe dementia. In the group receiving combined treatment with alpha-tocopherol and selegiline, the incidence of falls was 22 percent and that of syncope was 16 percent.

‡This test correlates with the cognitive subscale of the Alzheimer's Disease Assessment Scale,⁶¹ and the change shown would represent a 3 percent benefit as compared with placebo on this scale.

to recommend that they be given to patients in nursing homes. Data supporting long-term administration of cholinesterase inhibitors are limited to uncontrolled extension trials of tacrine,³⁸ donepezil,⁵¹ and eptastigmine.⁵² Whether tolerance to these drugs occurs during long-term administration is unknown. Because higher doses have the greatest benefits and the most adverse effects, gradual increases to the maximal tolerated dose have been recommended. Treatment can be continued indefinitely, but it is often discontinued because of decreasing tolerance of adverse effects or lack of efficacy. Patients and their families should be alerted to the possibility of deterioration in the patient's condition after discontinuation of treatment.^{28,42}

SLOWING THE PROGRESSION OF ALZHEIMER'S DISEASE

Alpha-Tocopherol and Selegiline

Alpha-tocopherol (vitamin E) limits free-radical formation, oxidative stress, and lipid peroxidation^{53,54} and promotes survival of cultured neurons exposed to β -amyloid.⁵⁵ Selegiline is a monoamine oxidase inhibitor with antioxidant properties that increases brain catecholamines. In the largest trial to date,⁵⁶ 341 patients with Alzheimer's disease were randomly assigned to receive either 2000 IU of alpha-tocopherol

per day, 10 mg of selegiline per day, both drugs, or placebo (Table 4). The times until institutional placement, loss of the ability to perform basic activities of daily living, severe dementia, or death were determined. The time until half of the patients reached one of these end points was 440 days in the placebo group, as compared with 655 days in the selegiline group, 670 days in the alpha-tocopherol group, and 581 days in the combined-treatment group. There were no differences among the groups in the score on the cognitive subscale of the Alzheimer's Disease Assessment Scale or any other cognitive-test score. Falls and syncope were more frequent among patients receiving either treatment than among those receiving placebo, and they were especially frequent among those receiving the combined treatment (Table 4). Selegiline should not be given with meperidine.

Idebenone

Idebenone, a benzoquinone derivative with antioxidant properties, has been used in Alzheimer's disease.⁶² In a six-month study that included 300 patients with Alzheimer's disease who were randomly assigned to receive a low dose (90 mg per day) or a high dose (270 mg per day) of idebenone or placebo, the high-dose group had a 2.8 percent decrease in the score on the cognitive subscale of the Alzhei-

mer's Disease Assessment Scale and the low-dose group a 0.8 percent decrease (Table 4).⁵⁷ There were no changes in the score on the Clinical Global Impression of Change scale in any group. Adverse effects included nausea, dizziness, headache, heartburn, angina, and an increase in serum aminotransferase concentrations, but few were serious.

Propentofylline

Propentofylline, a xanthine derivative, stimulates the synthesis and release of nerve growth factor in the basal forebrain.^{63,64} Among 170 patients with Alzheimer's disease who were randomly assigned to receive 900 mg per day of propentofylline or placebo, there was a decrease in cognitive-test score equivalent to a 3 percent increase in the score on the cognitive subscale of the Alzheimer's Disease Assessment Scale in the propentofylline group,⁵⁸ but no change in the score on the Clinical Global Impression of Change scale after 12 months (Table 4). In a total of 901 patients given propentofylline in other clinical trials, the scores on the Mini-Mental State Examination improved slightly, but the cognitive subscale of the Alzheimer's Disease Assessment Scale was not used in these trials.^{14,65} Adverse effects were infrequent but included nausea, dizziness, headache, and nonspecific gastrointestinal pain.

Ginkgo biloba

Extract of *Ginkgo biloba*, derived from the leaf of a subtropical tree, has putative antioxidant, neurotrophic, and antiinflammatory properties.⁶⁶ It is available in health-food stores. Among 236 patients with Alzheimer's disease who were randomly assigned to receive *Ginkgo biloba* or placebo for 12 months, there was a 2.4 percent decrease in the score on the cognitive subscale of the Alzheimer's Disease Assessment Scale (Table 4), but no differences in the score on the Clinical Global Impression of Change scale.⁵⁹ Only 50 percent of the patients in the *Ginkgo biloba* group completed the trial, as did only 38 percent of the placebo group. A meta-analysis of this and four other studies concluded that *Ginkgo biloba* improves cognitive function slightly.⁶⁷

Acetyl-L-Carnitine

Acetyl-L-carnitine, the acetyl ester of L-carnitine, is an intracellular carrier of acetyl groups across mitochondrial membranes⁶⁸ that promotes acetylcholine release, increases choline acetyltransferase activity, and is an antioxidant. It also is found in health-food stores. The results of clinical trials in patients with Alzheimer's disease have been inconsistent.^{60,69,70} In the largest study, in which 419 patients were randomly assigned to receive acetyl-L-carnitine or placebo for 12 months, there were no differences in the score on the cognitive subscale of the Alzheimer's Disease Assessment Scale or the Clinical Global Impression

of Change scale between the two groups (Table 4).⁶⁰ Adverse effects included body odor, increased appetite, and rash.

Social Interventions

An intensive program of family education and counseling was found to diminish the burden of caring for elderly family members with dementia.⁷¹ In a 3.5-year randomized trial comparing this intervention with referral to standard social services, the intensive program was associated with a delay of as much as 1 year in placement of the patient in a nursing home; the effect was similar to that reported for alpha-tocopherol and selegiline.⁷² However, the need for intensive training of personnel and care givers prevents this option from being readily available for most patients.

Efficacy of Treatments to Delay Disease Progression

Alpha-tocopherol and selegiline delay the development of the later stages of Alzheimer's disease, but it is difficult to say whether a delay of 20 to 30 weeks is meaningful in a disease that lasts a decade or more. Unlike selegiline, alpha-tocopherol does not interact with other drugs and therefore can be administered to the majority of patients, regardless of other treatments for Alzheimer's disease. The studies of idebenone, propentofylline, and *Ginkgo biloba* provide no clinically meaningful information on the basis of which to make treatment recommendations.

TREATMENT OF THE BEHAVIORAL MANIFESTATIONS OF ALZHEIMER'S DISEASE

Depression

Major depression occurs in 5 to 8 percent of patients with Alzheimer's disease.^{73,74} Up to 25 percent have depressed mood at the time of onset of memory loss.⁷⁵ Few studies of the use of antidepressant drugs in patients with Alzheimer's disease have been published, although these drugs are frequently used.⁷⁶ The effects of the tricyclic antidepressant imipramine were similar to those of placebo in alleviating depression in 61 patients with Alzheimer's disease (Table 5).⁷⁷ In a crossover study of 26 depressed patients with Alzheimer's disease, in which clomipramine and placebo were each given for six weeks, both treatments resulted in a 40 to 50 percent reduction in the score on the Hamilton Depression Rating Scale.^{78,92} Although the effect of clomipramine lasted longer,⁷⁸ it resulted in a decline in the score on the Mini-Mental State Examination. Other adverse effects included dry mouth in 91 percent of patients, dizziness in 64 percent, and sleep disturbance in 45 percent.

The serotonin-reuptake inhibitor citalopram resulted in a 20 percent greater improvement in the score on a depression rating scale than did placebo,

TABLE 5. DRUGS USED IN THE MANAGEMENT OF BEHAVIORAL MANIFESTATIONS OF ALZHEIMER'S DISEASE.

BEHAVIORAL PROBLEM	TYPES OF DRUG	STUDY	ESTABLISHED BENEFIT OVER PLACEBO IN PATIENTS WITH DEMENTIA	ADVERSE EFFECTS OCCURRING IN MORE THAN 10% OF PATIENTS USING THE DRUG
Depression	Tricyclic antidepressant drugs		No	Dry mouth, dizziness, impaired sleep, orthostatic hypotension, confusion, worsening of cognitive function
		Reifler et al. ⁷⁷		
		Petracca et al. ⁷⁸		
	Selective serotonin-reuptake inhibitors	Taragano et al. ⁷⁹	Yes	Insomnia, anorexia, ejaculatory failure, nausea, diarrhea
		Nyth and Gottfries ⁸⁰		
		Taragano et al. ⁷⁹		
Psychosis and delusions	Monoamine oxidase inhibitor	Katona et al. ⁸¹	Yes	Extrapyramidal signs, somnolence, peripheral edema, orthostatic hypotension
		Roth et al. ⁸²		
		Schneider et al. ⁸³	Yes	
	Neuroleptics	Petrie et al., ⁸⁴ Barnes et al., ⁸⁵ Finkel et al., ⁸⁶ Devanand et al. ⁸⁷		Extrapyramidal signs, tardive dyskinesia in standard doses. In a study comparing high-dose haloperidol (2 to 3 mg per day), low-dose haloperidol (0.5 to 0.75 mg per day), and placebo in 71 patients with Alzheimer's disease and psychosis or disruptive behavior, ⁸⁷ the high dose produced a 30 percent greater improvement than either placebo or the low dose. High-dose haloperidol treatment resulted in extrapyramidal signs in 20 percent of patients.
		Lavretsky and Sultzer, ⁸⁸ Katz et al. ⁸⁹		
		Tariot et al. ⁹⁰	No	
Agitation	Benzodiazepines	Tariot et al. ⁹¹	Yes	Sedation, ataxia, falls

*Paroxetine was compared with imipramine in Alzheimer's disease.

†Older neuroleptics such as thiorazine and thioridazine were also associated with acute confusion because of their anticholinergic effects.

with no effect on cognitive performance in 65 patients with Alzheimer's disease.⁸⁰ Six of the 65 patients in the citalopram group had adverse effects such as fatigue, drowsiness, orthostatic hypotension, and diminished libido and sexual function. Fluoxetine was compared with amitriptyline, another tricyclic antidepressant drug, in 37 patients.⁷⁹ Both reduced depression rating scores by 30 to 40 percent, but half of the amitriptyline group had confusion and disorientation, and 20 percent of the fluoxetine group withdrew because of nausea or diarrhea. The results and frequency of adverse effects were similar in an eight-week study comparing paroxetine and imipramine in 198 patients with depression and dementia.⁸¹

The monoamine oxidase inhibitor moclobemide resulted in a 27 percent greater decrease in depression rating scores than did placebo in a 42-day multicenter study of 694 patients with unspecified forms of dementia.⁸² Dizziness (3 percent) and nausea (3 percent) were significantly more frequent with moclobemide than with placebo.

Antidepressant drugs have similar efficacy. The choice of one over another should be based on their adverse effects. Some tricyclic antidepressant drugs, such as amitriptyline, have anticholinergic activity and can cause confusion or orthostatic hypotension. Selective serotonin-reuptake inhibitors are better tolerated but cause insomnia, anorexia, or ejaculatory failure in up to 5 percent of patients (Table 5).

Delusions and Psychosis

Delusions and psychotic behavior increase with the progression of Alzheimer's disease and, once present,

are persistent in 20 percent of patients. Agitation may coexist in up to 20 percent more patients, and it tends to increase with advancing disease.^{93,94} Symptoms resolve or diminish in about 20 percent more patients treated with neuroleptic drugs such as haloperidol than among patients given placebo,⁸³ but little evidence supports the use of one drug over another.⁸³⁻⁸⁸ Most neuroleptic drugs cause extrapyramidal signs and tardive dyskinesia in standard doses. In a study comparing high-dose haloperidol (2 to 3 mg per day), low-dose haloperidol (0.5 to 0.75 mg per day), and placebo in 71 patients with Alzheimer's disease and psychosis or disruptive behavior,⁸⁷ the high dose produced a 30 percent greater improvement than either placebo or the low dose. High-dose haloperidol treatment resulted in extrapyramidal signs in 20 percent of patients.

In a study of 12,000 residents in 60 long-term care facilities,⁹⁵ risperidone was found to be similar in terms of efficacy to both haloperidol and thioridazine, but effective doses of haloperidol or thioridazine were difficult to achieve because of adverse effects. In a 12-week multicenter, placebo-controlled trial involving 456 institutionalized patients with advanced Alzheimer's disease and psychosis, risperidone in doses ranging from 0.5 to 2 mg daily resulted in a reduction in symptoms without worsening of cognitive performance, as compared with placebo.⁸⁹ Extrapyramidal signs and somnolence occurred in 7 percent and 10 percent, respectively, of the patients given 0.5 mg daily and in 21 percent and 28 percent of those given 2 mg daily.

Aggression and agitation may be associated with

psychosis.^{96,97} Many drugs have been evaluated in open trials, including antidepressants, beta-adrenergic antagonists, lithium, benzodiazepines, and anticonvulsant drugs, with inconsistent results.^{90,98} In addition to producing sedation, many of these drugs worsen cognitive function, and they have been associated with falls and fractures.⁹⁹

Carbamazepine reduced agitation and hostility in 51 patients with Alzheimer's disease in a six-week trial.⁹² There was a 50 percent greater reduction in the amount of staff time required to care for patients given carbamazepine than for those in the placebo group, but adverse effects were more frequent. Valproic acid, another anticonvulsant drug given for agitation, has fewer adverse effects than carbamazepine, but no controlled trials of its efficacy in patients with Alzheimer's disease have been published.¹⁰⁰

Cholinergic Drugs and Behavioral Manifestations

Tacrine and metrifonate and the cholinergic agonist xanomeline may affect behavior in patients with Alzheimer's disease.^{23,43,101} Patients taking any of these drugs were less likely to have delusions or hallucinations than those taking placebo. Tacrine resulted in a 20 percent reduction in or stabilization of delusions,¹⁰¹ and xanomeline resulted in a 10 to 20 percent greater reduction in episodes of delusion, suspiciousness, fearfulness, agitation, or wandering than did the placebo.²³ Because improvement in behavioral manifestations was not a primary end point in these studies, none of the drugs can be recommended as treatment for patients with Alzheimer's disease.

Sleep Disturbance

With progression of Alzheimer's disease, there is a steady decline in the stages of rapid-eye-movement and non-rapid-eye-movement sleep and an increase in the percentage of time spent awake.¹⁰² Sleep disturbance is associated with "sundowning" — delirium that occurs during the evening or night and that disappears or improves during the daytime. Thirty percent of institutionalized patients and 10 percent of ambulatory patients with Alzheimer's disease have sleep disturbances, which may be related to degeneration in the brain stem.^{94,103} Treatments range from neuroleptic drugs to sedative drugs, all of which have adverse effects. Reducing daytime naps, restriction of time in bed, and exposure to bright light during waking hours may also be helpful, but these measures have not been rigorously investigated.¹⁰²

Wandering

Wandering away from the home or a health care facility can occur at any stage of Alzheimer's disease, and its frequency increases as cognitive function and independence in day-to-day activities decrease. One community study found that 36 percent of patients with Alzheimer's disease wandered.¹⁰⁴ Altering the

physical environment by concealing doorways and encouraging movement under supervision may limit wandering.^{104,105} A nationwide network called Safe Return has been created by the Alzheimer's Association.¹⁰⁶ A Safe Return identification item worn by the patient lists a nationwide, toll-free telephone number giving access to operators on call 24 hours a day, seven days a week. Thus, patients who are missing and those who are found by others can be reported and returned to their homes.

PREVENTION

The expected increase in the number of elderly people at risk for Alzheimer's disease and the projected costs involved have led to the consideration of preventive treatments. Prevention of Alzheimer's disease will require the development of safe treatments or interventions that could be used in a large number of elderly people at risk, many of whom might never have the disorder. On the basis of several ongoing lines of investigation, estrogen-replacement therapy,¹⁰⁶⁻¹⁰⁹ nonsteroidal antiinflammatory drugs,¹¹⁰ and a vaccine directed at amyloid production¹¹¹ are under consideration as potential preventive treatments.

CONCLUSIONS

Current treatments for patients with Alzheimer's disease target the biochemical pathway that is associated with the disease and is considered amenable to modification. Molecular approaches that modify the effects of mutations in critical genes or that lessen genetic susceptibility need to be developed. Therapeutic approaches should focus on methods to prevent or delay the progression of Alzheimer's disease. The development of such approaches will depend on increasing our knowledge of the pathophysiology of the disease.

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