

Treatment Guidelines for Alzheimer's Disease: Redefining Perceptions in Primary Care

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Background: Current treatment guidelines for Alzheimer's disease (AD) do not reflect more recently collected data on therapeutic outcomes other than cognitive function and memory, and this has led to a limited understanding of the value of drug therapy in AD.

Objectives: To evaluate the need to revise treatment guidelines for AD, to review data that have become available since the publication of current guidelines, and to communicate how existing guidelines and relevant new data can be valuable to the primary care provider who assesses and treats patients with AD.

Data Sources: A MEDLINE search was conducted to identify existing treatment guidelines using the MeSH headings *Alzheimer disease–drug therapy* AND *practice guidelines*. The alternative terms *treatment guidelines*, *practice parameter*, and *practice recommendation* were also searched in conjunction with the MeSH term *Alzheimer disease–drug therapy*. Additionally, MEDLINE was searched using the term *dementia* and publication type “practice guideline.” All searches were limited to articles published within the last 10 years, in English. A total of 116 articles were identified by these searches. Additional publications were identified by manually searching the reference lists of these articles and of published clinical trials of AD therapies.

Study Selection and Data Extraction: Current AD treatment guidelines and clinical trial results for AD treatment options were extracted, reviewed, and summarized to meet the objectives of this article.

Data Synthesis: Current guidelines support the use of cholinesterase inhibitors in patients with mild to moderate AD. More recent clinical research indicates that cholinesterase inhibitor treatment provides effectiveness across a wide range of dementia severity and multiple symptom domains. These medications also significantly decrease caregiver burden and may lower the risk for nursing home placement.

Conclusions: The expanding literature on AD medications suggests that treatment guidelines need to be reexamined. Recent data emphasize preservation of abilities and delay of adverse outcomes in AD patients rather than short-term improvements in cognitive test scores. Treatment appears to provide the greatest benefit when it is initiated early in the course of the disease and maintained over the long term. Revised treatment guidelines should address newer medications and more recent outcomes considerations, as well as provide guidance on how long to continue and when to discontinue pharmacotherapy for AD.

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Alzheimer's disease (AD) is a very common condition. It is estimated to affect 6% to 10% of the population over age 65 in the United States. Its prevalence is expected to rise dramatically through the middle of the 21st century. Results from one epidemiologic study projected that there were 4.5 million people in the United States with AD in 2000. An extrapolation of these results that accounts for the continued aging of the population suggested that the number of AD patients in the United States will reach 13.2 million by 2050.¹ Not surprisingly, the economic burden of AD is very high. Annual costs for AD and other dementias were estimated at \$100 billion in the United States in 1997.² The overall cost of dementia to U.S. society is therefore similar to that of diabetes mellitus. More recently, it has been estimated that the total direct and indirect costs associated with AD alone are \$88.3 billion, with per-patient costs of \$91,000 over the course of the illness.³

Alzheimer's disease is a neurodegenerative disorder characterized by abnormalities in multiple brain regions, including the neocortex, entorhinal area, hippocampus, amygdala, nucleus basalis, anterior thalamus, and monoaminergic projections from brainstem nuclei.^{4,5} The neuropathologic changes characteristic of AD are progressive, and their magnitude correlates with clinical disease severity. Involvement of the cholinergic system in AD was initially suggested by the postmortem observation of substantial neocortical deficits in the enzyme responsible for the synthesis of acetylcholine, choline acetyltransferase. Loss of cholinergic neurons is well documented in patients who have died with AD. Acetylcholine plays a key role in learning and memory, and the predictable cholinergic changes observed in patients with AD led to the “cholinergic hypothesis” to explain the symptom

pattern of AD. In this model, degeneration of cholinergic neurons in the basal forebrain and the associated loss of cholinergic neurotransmission in the cerebral cortex, especially in the hippocampus, contributes significantly to the deterioration in cognitive function seen in patients with AD.⁶⁻⁸ The focus on hippocampal acetylcholine input in the cholinergic hypothesis may account for the historical bias toward memory improvement as the desired outcome from AD therapeutics.

Excessive glutamate levels in the cerebral cortex of AD patients have also been hypothesized to contribute to learning and memory deficits in AD. Memantine, a moderate-affinity *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist, is postulated to counteract this effect.⁹ Memantine has demonstrated efficacy in moderate to severe AD, but appears to have less consistent effects in mild AD,¹⁰ and it has not been approved in the United States for use in patients with mild dementia. The reasons for differences in efficacy by stage are unknown, but may be related to increasing dysfunction in glutamate regulation with more advanced disease.¹¹

As AD progresses, patients experience deterioration across multiple domains, including cognition, function, and behavior, but the specific symptoms vary between patients and between stages. This variability means that treatment targets will need to be revisited and reconsidered across the stages of the disease. Mild AD (often associated with Mini-Mental State Examination [MMSE] scores ≥ 20) is characterized by forgetfulness and difficulties with activities such as driving, shopping, and hobbies. Patients with mild AD may also be at increased risk for depression. Moderate AD (MMSE score $\approx 10-19$) is reflected by marked memory loss and a requirement for significant assistance with activities of daily living (ADLs). Patients with moderate AD may also exhibit wandering, insomnia, and delusions. Severe AD (MMSE score < 10) is characterized by limited language, loss of basic ADLs, agitation, and incontinence.^{12,13}

METHOD

Treatment guidelines were identified via a MEDLINE search using the MeSH headings *Alzheimer disease-drug therapy* AND *practice guidelines*. The alternative terms *treatment guidelines*, *practice parameter*, and *practice recommendation* were also searched in conjunction with the MeSH term *Alzheimer disease-drug therapy*. Additionally, MEDLINE was searched using the term *dementia* and publication type "practice guideline." All searches were limited to articles published within the last 10 years, in English. A total of 116 unique articles were identified. The reference lists of articles thus identified were searched manually to identify additional articles of interest.

CURRENT GUIDELINES FOR THE TREATMENT OF PATIENTS WITH ALZHEIMER'S DISEASE

Although treatment guidelines have been published for Japan in 2004¹⁴ and Italy in 2005,¹⁵ the most current clinical guidance for physicians treating patients with AD in the United States was published in 2001, when the Quality Standards Subcommittee of the American Academy of Neurology published 3 practice parameters: early detection of dementia,¹⁶ diagnosis of dementia,¹⁷ and management of dementia.¹⁸ These papers were subsequently abstracted and summarized by the American Geriatrics Society Clinical Practice Committee.¹⁹ The primary management question these evidence-based guidelines addressed was whether a treatment "improve[s] outcomes in patients with dementia compared with no treatment."¹⁸ The data available at that time to answer this question were limited—the guidelines cite 6 randomized, controlled clinical trials of cholinesterase inhibitors (ChEIs). Many more such data are available today (Table 1), and other controlled studies have been published using a variety of outcome measures and trial designs to evaluate important aspects of AD treatment beyond standardized efficacy assessments. The purpose of this article is to review these studies and highlight clinical data that are important to providing the best possible treatment for patients with AD in primary care.

THERAPEUTIC OPTIONS FOR ALZHEIMER'S DISEASE

Cholinesterase inhibitors have been the cornerstone of treatment for patients with AD for over a decade.^{18,39} Four drugs in this class, donepezil, galantamine, rivastigmine, and tacrine, are approved for the treatment of mild to moderate AD, and they are recommended by the American Academy of Neurology practice parameter¹⁸ as standard of care for treatment of patients with this condition (Table 2). Tacrine was approved for the treatment of AD in 1993, but is now rarely used because of a difficult dosing regimen, poor tolerability, and significant hepatotoxicity. Donepezil was approved for treatment of mild to moderate AD in 1996, rivastigmine was approved in 2000, and galantamine was approved in 2001. Memantine, an NMDA receptor antagonist, was approved for the treatment of moderate to severe AD in 2003 (Table 2). Memantine has also been studied as adjunctive therapy in patients with moderate to severe AD who were being treated with donepezil.³⁶

The ChEIs have repeatedly shown sustained, clinically meaningful benefit in double-blind, placebo-controlled trials.⁴⁰ Review of their effectiveness in comparison with placebo suggests that the more recently developed ChEIs (rivastigmine, galantamine) have no greater clinical benefit than donepezil. No adequately controlled long-term

Table 1. Positive Placebo-Controlled Studies of Treatment Options for Alzheimer's Disease

Reference	Agent	Dose(s) Studied (mg/d)	N	Duration (wk)	Positive Outcome Measures
Early Alzheimer's disease					
Seltzer et al, 2004 ²⁰	Donepezil	5–10	153	24	Modified ADAS-cog, MMSE
Mild to moderate Alzheimer's disease					
Knapp et al, 1994 ²¹	Tacrine	160	663	30	ADAS-cog CIBIC-Plus FCCA
Rogers et al, 1996 ²²	Donepezil	1, 3, 5	161	12	ADAS-cog MMSE
Rogers et al, 1998 ²³	Donepezil	5–10	468	12	Patient QOL ADAS-cog CIBIC-Plus MMSE
Rogers et al, 1998 ²⁴	Donepezil	5–10	473	24	ADAS-cog CIBIC-Plus MMSE
Burns et al, 1999 ²⁵	Donepezil	5–10	818	30	CDR-SB ADAS-cog CIBIC-Plus
Winblad et al, 2001 ²⁶	Donepezil	5–10	286	52	CDR-SB PDS GBS
Corey-Bloom et al, 1998 ²⁷	Rivastigmine	1–4, 6–12	699	26	ADAS-cog CIBIC-Plus PDS
Rosler et al, 1999 ²⁸	Rivastigmine	1–4, 6–12	725	26	ADAS-cog CIBIC-Plus PDS
Farlow et al, 2000 ²⁹	Rivastigmine	1–4, 6–12	545	26	ADAS-cog
Wilcock et al, 2000 ³⁰	Galantamine	24, 32	653	26	ADAS-cog CIBIC-Plus DAD
Raskind et al, 2000 ³¹	Galantamine	24, 36	653	26	ADAS-cog CIBIC-Plus
Tariot et al, 2000 ³²	Galantamine	8, 16, 24	978	21	ADAS-cog CIBIC-Plus ADCS-ADL NPI
Brody et al, 2005 ³³	Galantamine prolonged release	16–24	971	26	ADAS-cog (11 item) ADCS-ADL
Moderate to severe Alzheimer's disease					
Feldman et al, 2001 ³⁴	Donepezil	5–10	290	24	CIBIC-Plus sMMSE SIB DAD FRS NPI
Reisberg et al, 2003 ³⁵	Memantine	20	252	28	CIBIC-Plus ADCS-ADLsev SIB
Tariot et al, 2004 ³⁶	Memantine (added to stable donepezil regimen)	20	404	24	SIB ADCS-ADL (19 item) CIBIC-Plus NPI BGP-care dependency
Severe Alzheimer's disease					
Feldman et al, 2005 ^{37a}	Donepezil	5–10	145	24	CIBIC-Plus sMMSE SIB DAD NPI
Winblad et al, 2006 ³⁸	Donepezil	5–10	248	24	SIB ADCS-ADLsev MMSE CGI-I

^aPost hoc subanalysis of data reported in Feldman et al.³⁴

Abbreviations: ADAS-cog = Alzheimer Disease Assessment Scale-cognitive subscale, ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory, ADCS-ADLsev = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory modified for severe dementia, BGP = Behavior Rating Scale for Geriatric Patients, CDR-SB = Clinical Dementia Rating-Sum of the Boxes, CGI-I = Clinical Global Impressions-Improvement scale, CIBIC-Plus = Clinician's Interview-Based Impression of Change-plus caregiver input, DAD = Disability Assessment for Dementia, FCCA = Final Comprehensive Consensus Assessment, FRS = Functional Rating Scale, GBS = Gottfries-Bråne-Steen Scale, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, PDS = Progressive Deterioration Scale, QOL = quality of life, SIB = Severe Impairment Battery, sMMSE = standardized Mini-Mental State Examination.

Table 2. Treatment Options for Alzheimer's Disease

Drug	Description	Mechanism of Action	Approved Indication
Tacrine	Reversible ChEI	Elevates acetylcholine concentration and slows degradation by cholinergic neurons	Mild to moderate dementia of the Alzheimer's type
Donepezil	Reversible, selective ChEI	Increases acetylcholine concentration by reversible, selective inhibition of hydrolysis by acetylcholinesterase	Mild to moderate dementia of the Alzheimer's type
Rivastigmine	Reversible ChEI	Increases acetylcholine concentration by reversible inhibition of hydrolysis by acetylcholinesterase	Mild to moderate dementia of the Alzheimer's type
Galantamine	Reversible, competitive ChEI	Increases acetylcholine concentration by reversible, selective inhibition of hydrolysis by acetylcholinesterase; allosterically modulates nicotinic acetylcholine receptors	Mild to moderate dementia
Memantine	Noncompetitive NMDA receptor antagonist	Binds preferentially to the NMDA-receptor cation channels	Moderate to severe dementia of the Alzheimer's type

Abbreviations: ChEI = cholinesterase inhibitor, NMDA = *N*-methyl-D-aspartate.

head-to-head trials have been reported. Memantine has shown clinical benefit in more advanced disease^{35,36,41}; these studies were published subsequent to the most recent guidelines. Recently, the U.K. National Institute for Health and Clinical Excellence released a guidance statement⁴² based on a combination of clinical and economic analyses stating that the ChEIs are appropriate for treatment of moderate-stage AD. This overturned their preliminary opinion that current treatment options offer no clinical benefits—an opinion hotly refuted by many physicians and patient/caregiver advocates. Nonetheless, many physicians still do not believe that there are meaningful treatment options for patients with AD.

REDEFINING TREATMENT SUCCESS

There are currently no means for reversing the pathologic processes of AD. Therefore, the specific goals of therapy are to preserve cognitive and functional ability, minimize behavioral disturbances, and slow disease progression,³⁹ with maintenance of the patient's (and caregiver's) quality of life. Much of the criticism of the ChEIs can be attributed to biased or uninformed perceptions of what therapy should be accomplishing rather than an absence of effect in well-conducted clinical trials. The impact of ChEI treatment has most often been measured in terms of effects of these medications on cognition and memory; however, patients and caregivers view the benefits of these treatments much more broadly than most physicians. Analysis of results from a trial of donepezil in 108 patients with mild to moderate AD indicated that patients and caregivers set different treatment goals than physicians. Patients and caregivers tended to identify solutions to specific problems (e.g., reduction in repetitive questions, decreased need for lists and routines) as targets for therapy while physicians grouped many distinct problems under a single treatment goal of improved memory. In addition, patients and their caregivers set more goals

than physicians did with respect to leisure, social interaction, behavior, and function.⁴³

It is becoming increasingly recognized that efficacy measures used to evaluate responses to ChEIs do not capture the full benefit of these treatments. The instruments used in clinical trials are required for regulatory approval of the drugs. They are based on historical preconceptions of what is important to study rather than on meeting genuine patient needs, and they do not translate well to clinical practice settings. Results from a survey of physicians who care for patients with AD indicated that physicians recognize benefits of therapy (e.g., cognitive activation, attention, ability to carry out leisure activities, reduced requirement for repetition) that are not captured by instruments currently used to assess outcomes in clinical trials.⁴⁴ Capturing these effects of treatment is important for comparison of therapies as well as for their potential to increase our understanding of the physiologic basis of the symptoms in AD.⁴⁴ Outcomes meaningful to patients and families, such as quality of life, preservation of personality and function, and contributions to family life, are exceptionally difficult to measure because they are so individual-specific. Therefore, it seems most reasonable to weight functional abilities, behavioral problems, caregiver burden, and health care resource utilization more heavily in evaluation of therapies for AD.

Although current guidelines discuss functional and behavioral outcomes, increased emphasis should be placed on the ability of treatments to slow the progressive changes in all of these measures.⁴⁵ A response to treatment in patients with this condition may be best defined as long-term stabilization or less than expected decline rather than a transient improvement from baseline.⁴⁵ As the American Academy of Neurology guidelines point out, global improvements in cognition, function, and behavior were detectable, indicating that the changes detected on standardized assessments were clinically meaningful.¹⁸ Therefore, global assessments such as the Clinician's

Interview-Based Impression of Change-plus caregiver input (CIBIC-Plus) and Clinician's Global Impression of Change may be more clinically translatable outcome measures than cognitive scales. Additionally, research using important practical measures (for example, time to nursing home placement, functional decline, or other defined outcome) should be incorporated into the guidelines and considered by primary care providers when making treatment decisions.

EVIDENCE SUPPORTING CURRENT GUIDELINES

The ChEIs have a broad base of evidence from randomized, double-blind, placebo-controlled trials that supports their utility across a wide range of clinically meaningful outcomes. The "regulatory"-type studies are summarized in Table 1. In addition to effects on cognition, these drugs have demonstrated significant effects on measures of behavior, ADLs, and global patient function. Some positive effects have been seen on measures of cognition, ADLs, and global function in severe AD with memantine,^{35,36,41} but because it is a newer agent, fewer outcomes have been studied.

There have been 3 recent meta-analyses of clinical results obtained with ChEIs in patients with AD. Trinh and colleagues⁴⁶ evaluated 29 parallel-group or crossover, randomized, double-blind, placebo-controlled trials of outpatients with mild to moderate AD who were treated for ≥ 1 month. Their analysis indicated that ChEI treatment had statistically significant modest benefits with respect to neuropsychiatric and functional outcomes. A second meta-analysis of 16 trials indicated that the placebo-corrected global and cognitive "response" rates were 9% and 10%, respectively, with a placebo-corrected adverse event rate of 8%.⁴⁷ This analysis indicated that the numbers of patients needed to treat to achieve 1 global response and 1 cognitive response and to cause an adverse event in 1 patient were 12, 10, and 12, respectively.⁴⁷ However, a global response was defined as improvement on the Clinician's Global Impression of Change, and a cognitive response was defined as an improvement of 4 points or more on the Alzheimer Disease Assessment Scale-cognitive subscale. This definition of response does not account for patients who show less than expected decline, another clinically important outcome of treatment. Whitehead and associates⁴⁸ carried out a meta-analysis of results for donepezil that focused on phase II and III double-blind, placebo-controlled trials up to 24 weeks in duration that were completed by the end of 1999. Cognitive performance and CIBIC-Plus scores were better in patients treated with donepezil than in those receiving placebo ($p \leq .001$ for both the 5- and 10-mg doses; odds ratio [OR] = 1.77 and 1.90, respectively). Results obtained with 10 mg/day of donepezil were significantly superior to those with the 5-mg/day dose ($p = .005$).⁴⁸

A more comprehensive, global view of AD treatment should focus on delaying outcomes rather than on improving performance on cognitive tests. A good example contrasting these ways of thinking about AD outcomes is the recent investigation of donepezil for amnesic mild cognitive impairment, a condition that has been shown to be associated with high risk for conversion to AD. A 24-week trial designed to demonstrate improvement on a cognitive test, the NYU Paragraph Recall test, failed to detect a significant effect⁴⁹; however, a 3-year donepezil trial designed to detect differences in the rate of progression from mild cognitive impairment to AD found that treatment with donepezil delayed this transition, at least early in the observation period.⁵⁰

EVIDENCE SUPPORTING EXPANSION OF CURRENT GUIDELINES

How Long to Treat?

Guidelines published in 2001 did not have the benefit of subsequently published studies with longer duration and patient populations with more advanced AD. As patients being treated for AD continue to progress (at an apparently slower rate than they would without treatment), physicians have heard multiple opinions about the value of maintaining these treatments into more advanced stages of AD. Open-label extension studies of placebo-controlled clinical trials indicate that patients appear to benefit from these treatments for several years.⁵¹⁻⁵⁸ Sustained benefit has been indicated in studies of up to 5 years' duration.^{51,58} Studies in patients with moderate to severe and severe AD are summarized in Table 1.

Other outcomes are also important in considering how long to continue treatment. For example, the 3-year risk for placement in a nursing home for patients with dementia has been estimated as 52%.⁵⁹ Dependencies in ADLs, high cognitive impairment, and the presence of 1 or more difficult behaviors all increase this risk.⁵⁹ Several studies have shown that persistent long-term treatment with a ChEI significantly decreases the risk for nursing home placement. Results from a cohort of 270 patients (135 taking a ChEI and 135 otherwise matched patients who were not) indicated that active treatment decreased the risk for nursing home placement from 41.5% to 6% over an average of 36.7 months of follow-up ($p < .0001$).⁶⁰ An analysis of dementia-related nursing home placement for 671 patients who were treated with donepezil in 1 of 3 randomized, double-blind trials found that donepezil dose and time on treatment were significantly correlated with time to first nursing home placement. Patients who received < 5 mg/day of donepezil or placebo during a double-blind trial and who failed to complete open-label extension studies of 24 to 96 weeks had an average time to institutionalization of 44.7 months. Those who received ≥ 5 mg/day of donepezil with $\geq 80\%$ compliance

during both double-blind treatment and 24- to 96-week open-label extensions had an average time to nursing home placement of 66.1 months ($p < .01$).⁶¹ In a long-term, double-blind, placebo-controlled study conducted in the United Kingdom, no effect of donepezil on nursing home placement was detected, but low enrollment, methodological issues, and societal differences in health care delivery limit the extent to which these findings can be generalized.⁶²

Most recently, Lopez et al.⁶³ showed that treatment with a ChEI for at least 12 months slows AD progression (OR for MMSE score change ≤ 2 at 1 year of follow-up = 2.32; $p = .001$ compared with no treatment) and that this slower progression is associated with significantly decreased risk for nursing home placement over 2 and 3 years of follow-up (1% vs. 16%, $p = .001$; and 11% vs. 50%, $p = .001$, respectively). (Most patients in this study who were treated with ChEIs [N = 135] took donepezil [N = 130], but some patients took tacrine [N = 22] or rivastigmine [N = 6]. Some patients switched drugs and therefore took more than 1 ChEI.) A retrospective analysis of a large U.S. medical claims database also supports the effectiveness of ChEI treatment in decreasing the risk for nursing home placement. Over a follow-up period of 27 months, 3.7% of 1181 patients who received rivastigmine, 4.4% of 3864 patients treated with donepezil, and 11.0% of 517 patients who did not receive a ChEI were placed in nursing homes.⁶⁴

Taken together, these studies indicate that long-term use of ChEIs may help AD patients live longer in community settings, with associated personal, social, and economic benefits. Similar data on memantine are not currently available. Recent evidence⁶⁵ from imaging studies suggests a possible anatomic basis for the slowed progression reported by Lopez and colleagues. In a 24-week randomized, double-blind, placebo-controlled study, patients who received donepezil (N = 34) had a mean total hippocampal volume loss of 0.4%, compared with 8.2% in patients who received placebo (N = 33; $p < .01$). Levels of *N*-acetylaspartate, a marker of neuronal viability and/or function, were also increased with donepezil treatment in some brain regions.⁶⁵ A prospective cohort study⁶⁶ also found that donepezil decreased the rate of hippocampal atrophy compared with untreated control subjects (3.82%, N = 54 vs. 5.04%, N = 93). This effect was statistically significant in an analysis of covariance model controlling for age, sex, disease duration, education, MRI interval, APOE genotype, and baseline cognitive assessment scores.⁶⁶ Furthermore, a randomized, double-blind, placebo-controlled pilot study⁶⁷ in 28 patients found that donepezil treatment stabilized glucose metabolism in some brain regions. The treatment difference at week 24 was significant for average glucose metabolism in the striatal axial slice (-0.5% vs. -10.4%; $p = .014$) and for regional glucose metabolism in predetermined regions of

interest in the right parietal lobe (6.8% vs. -5.3%; $p = .030$), left temporal lobe (1.7% vs. -7.6%; $p = .045$), and right and left frontal lobes (2.8% vs. -9.7%, $p = .016$ and 0.4% vs. -8.3%, $p = .042$, respectively).⁶⁷

Preserving ADL Function

Current guidelines recognize that preventing or delaying further loss of ADL function is an important goal of AD therapy and that ChEIs help to maintain ADL function.¹⁸ Although it is unrealistic to expect most patients to regain ADLs they have lost, it is reasonable to expect slowed or delayed functional decline. Significant preservation of ADL function compared with placebo has been shown for donepezil,^{25,26,34} galantamine,^{30,32,33,68,69} and rivastigmine.^{27,28,70,71} Memantine has also demonstrated benefits in ADLs.^{35,36,41} In a year-long study, patients taking donepezil were shown to retain levels of ADL function significantly longer than patients given placebo (a 5-month average delay to functional decline).⁷²

Reducing Problem Behaviors

Personality changes, mood disturbances, and even psychosis are frequently observed in patients with AD and are associated with more rapid cognitive and functional declines.⁷³ Difficult behaviors increase the risk of nursing home placement.⁵⁹ Problem behaviors in AD have also been associated with increased time and stress burden,^{74,75} higher rates of depression,⁷⁶ and reduced employment⁷⁷ among caregivers of AD patients. Patients treated with ChEIs and/or memantine may evidence behavioral benefits as reduced severity of existing behavioral disturbances and a lower incidence of new behavioral symptoms.

Studies of donepezil and galantamine using the Neuropsychiatric Inventory (NPI) have shown short-term behavioral improvement or stabilization.^{32,34,78} Donepezil has been shown to reduce the severity of neuropsychiatric symptoms in 134 patients with mild to moderate AD and marked neuropsychiatric symptoms at baseline (NPI score of at least 11 points). These patients were treated on an open-label basis for 12 weeks (6 weeks with 5 mg/day of donepezil followed by 10 mg/day for an additional 6 weeks). During the open-label phase, total scores were significantly reduced from baseline (mean score, 15.2 at week 12 vs. 25.4 at baseline; $p < .0001$). All domains of the NPI with the exception of elation were also significantly improved from baseline during this phase of treatment (all $p < .05$). The patients were then randomly assigned to either continue donepezil treatment or switch to placebo. The patients who continued on donepezil treatment for 12 weeks experienced significant improvements in NPI (treatment difference, 6.2 points; $p = .02$) compared with those switched to placebo, who experienced significant worsening.⁷⁹ Galantamine stabilized NPI scores over 5 months and reduced the incidence

of new problematic behaviors.⁸⁰ Rivastigmine may improve or prevent disruptive behavioral symptoms and may reduce the need for concomitant psychotropic medication.⁸¹ A trial of memantine monotherapy in moderate to severe AD showed no significant difference from placebo-treated patients on the NPI over 28 weeks.³⁵ In another trial, adding memantine to a stable donepezil regimen in patients with moderate to severe AD resulted in significantly less behavioral disturbance than in patients treated with donepezil only.³⁶

Reducing Caregiver Burden

Caregivers experience significant stress, which may affect their own health.⁸² Results from several studies have demonstrated that treatment with a ChEI decreases AD caregiver burden. Results from a 24-week double-blind, placebo-controlled study of 290 patients with moderate to severe AD (baseline standardized MMSE score, 5–17) indicated that donepezil treatment significantly reduced caregiver time spent assisting patients with basic and instrumental ADLs (–52.4 minutes/day, $p < .005$).⁸³ Similarly, in a year-long study, caregivers of donepezil-treated patients spent less time assisting patients with ADLs than caregivers of patients in the placebo group.⁸⁴ Data from a small study of rivastigmine ($N = 43$) were used to estimate that rivastigmine treatment saved caregiver time—up to 690 hours over 2 years—that would have been spent assisting with ADLs.⁸⁵ These studies indicate that AD therapy is associated with the important benefit of reduced caregiver stress.

SUMMARY

ChEI treatment has significant and meaningful direct benefit for AD patients, decreases the risk for nursing home placement, and reduces caregiver burden. While current guidelines support the use of ChEIs in patients with mild to moderate AD, results from more recent clinical trials indicate that ChEI treatment may also be effective across all stages of AD, as well as for mild cognitive impairment. Nevertheless, these drugs are still underutilized, partly because physicians underestimate the value of treatment to patients and caregivers. Physicians should consider the goals voiced by patients and their caregivers when evaluating the effectiveness of treatment.

Current treatment guidelines for use of ChEIs need to be revised and expanded. ChEI treatment is effective in patients across the spectrum of AD severity, but it has often been viewed in the acute therapeutic model: a drug is given and the patient should improve. In this model, failure to improve from baseline represents failure of therapy. However, the impact of ChEI therapy on disease progression in patients with, and at risk for, AD suggests that ChEIs should be viewed more like antihypertensives and lipid-lowering agents for decreasing the risk for cardio-

vascular events. If maintaining a person at the highest possible level of function is the goal of treatment, then long-term therapy with these agents should be most beneficial when initiated early in the course of the disease and maintained with good patient compliance over the long term. As new guidelines for the treatment of AD are developed, current data strongly support a change in emphasis to consider the utility of ChEIs, not as a treatment approach designed purely to relieve symptoms, but rather as a chronic treatment that reduces the progression and associated burden of a chronic disease.

Drug names: donepezil (Aricept), galantamine (Razadyne), memantine (Namenda), rivastigmine (Exelon), tacrine (Cognex).

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