Navigating Patients and Caregivers Through the Course of Alzheimer's Disease

Peter M. Aupperle, M.D., M.P.H.

Alzheimer's disease (AD) prevalence rates in the United States are expected to triple over the next 50 years, a consequence of the overall aging of the U.S. population. Because of the profound and far-reaching impact of AD, this projected increase in prevalence is expected to pose a tremendous challenge. Alzheimer's disease results in the cognitive and functional deterioration of the affected patient, and behavioral disturbances frequently accompany the disease. Furthermore, because of its progressive and debilitating nature, AD takes a dramatic emotional, physical, and financial toll on the patient's primary caregiver. Nonetheless, despite the burden experienced by both patients and caregivers, strategies for minimizing the negative consequences of AD are well characterized. Central to the successful management of AD is the prompt and accurate diagnosis of the disease, with current guidelines calling for a 2-tiered approach in which patients first undergo screening using a brief cognitive assessment tool, followed by a comprehensive battery of physical, psychological, and neurologic tests if signs of possible cognitive impairment are evident upon screening. Once a conclusive diagnosis of AD has been made, the development of a disease management approach targeting the needs of the patient and his or her caregiver becomes a primary concern. Pharmacologic interventions may play an important role in such approaches, as agents such as cholinesterase inhibitors and the *N*-methyl-D-aspartate receptor antagonist memantine have been associated with favorable outcomes for patients and caregivers alike. However, in addition to the therapeutic benefits of these agents, associated side effects and potential drug-drug interactions must also factor into decisions regarding the pharmacologic treatment of AD.
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The association between Alzheimer's disease (AD) and old age is an undeniable one, as almost all cases of this condition are found in individuals older than 65 years. The likelihood of developing AD is positively correlated with age, such that the AD risk in each 5-year age cohort starting with ages 65 to 70 years is roughly double that of the preceding 5-year age cohort.[1]

According to an estimate published in 2003, the prevalence of AD in the United States was approximately 4.5 million in the year 2000, and it is projected that this figure will nearly triple by 2050, an increase driven by the overall aging of the U.S. population.[2] Such an explosion in the prevalence of AD would be expected to pose a tremendous challenge, given the devastating and far-reaching impact of the disease. Alzheimer's disease is a condition that, in addition to profoundly altering the mental and physical state of the affected patient, also takes a dramatic toll on the patient's primary caregiver. Patients with AD experience cognitive and functional deterioration, often accompanied by behavioral disturbances, while caregivers see their quality of life reduced as a result of the daunting emotional, physical, and financial challenges that come with the task of caring for an individual—typically a spouse or a parent—who is becoming progressively less able to care for himself or herself.

While AD has substantial detrimental effects on patients and their caregivers, interventions exist that can minimize the negative consequences of AD for all involved. For example, currently available pharmacotherapeutic agents have been shown to slow the symptomatic progression of AD, thereby providing cognitive and functional benefits to affected patients and improving caregiver quality of life. Nonetheless, the beneficial effects of these agents cannot be realized in a given patient unless the presence of AD is recognized. Therein lies a significant challenge for clinicians, as it is believed that only about 60% of Americans who meet the criteria for a clinical diagnosis of AD have actually been diagnosed with this condition.[3] Therefore, it is clear that current efforts aimed at reducing the burden of AD must start with proper diagnosis.

DETECTION OF AD

Clinical Presentation

As a first step toward being able to identify cases of AD more reliably, it is important for clinicians to be familiar

From the Division of Geriatric Psychiatry, Robert Wood Johnson Medical School, Piscataway, N.J.
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Corresponding author and reprints: Peter M. Aupperle, M.D., M.P.H., Director, Division of Geriatric Psychiatry, Robert Wood Johnson Medical School, 667 Hoes Lane, Piscataway, NJ 08855 (e-mail: aupperpm@umdnj.edu).

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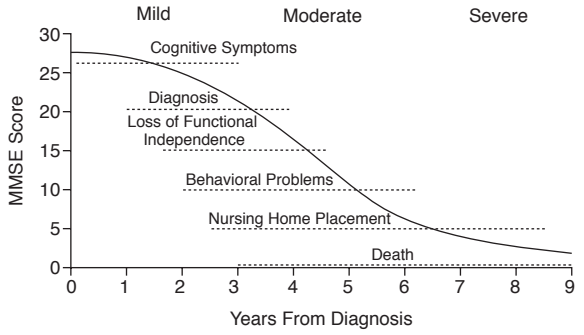
with the clinical presentation of the disease in its various stages. Because AD is a progressive condition, its earliest clinical stages are typically characterized by mild cognitive impairments such as forgetfulness and the inability to learn new information and by impairments in the performance of relatively complex everyday tasks (e.g., management of household finances, meal planning, telephone use). With regard to neuropsychiatric symptoms, signs of anxiety or depression may also suggest the presence of mild AD.[1,4]

As AD progresses to its moderate stages, cognitive and functional symptoms become more pronounced, and patients typically show impairment in short- and long-term memory as well as in the ability to perform more basic activities of daily living (ADLs), such as showering and toileting. In addition, deficits in intellect and reasoning (manifested in the form of poor judgment and inappropriate behavior) become more evident in patients at this stage of the disease. Affected patients are also increasingly likely to exhibit behavioral disturbances, with nearly half of all patients with moderate AD showing symptoms such as agitation, delusions, hallucinations, and wandering.[1,4]

In the late stages of AD, affected patients become almost completely reliant on others for their care. Severe AD is characterized by difficulties with all essential ADLs, and patients may also experience impairments in the ability to walk. Behavioral disturbances continue to be a common problem in this stage of the disease, and patients may also exhibit an inability to recognize family members. Furthermore, the capacity for verbal communication may become dramatically diminished in patients with severe AD, as groaning, screaming, mumbling, and other forms of incomprehensible speech are commonplace late in the course of the disease. As a result of these incapacitating symptoms, patients with late AD may be confined to bed for the overwhelming majority of their time, and death ultimately occurs either as a direct consequence of the disease or as a result of some AD-related adverse event, such as pneumococcal infection.[1]

Above all, AD is a degenerative condition, the symptoms of which are less evident early in the course of the disease but increase in number and severity as time goes on. A diagram of the typical symptomatic course of AD can be seen in Figure 1.[5]

Figure 1. Typical Symptomatic Course of Alzheimer's Disease[a]



[a]Reprinted from Feldman and Gracon[5] with permission from Taylor & Francis.
Abbreviation: MMSE = Mini-Mental State Examination.

Screening

Manageable strategies for the prompt recognition of AD rely on the use of an appropriate system for determining which individuals should undergo diagnostic testing for the disease. Because AD risk increases with age, contemporary guidelines call for a brief AD screening evaluation to be administered to all patients aged 80 years or older, and these same guidelines state that AD screening should also be performed for any patient aged 65 years or older whose clinical presentation is suggestive of cognitive impairment.[6]

The AD screening process generally entails the rapid gathering of information regarding the patient's cognitive status so that a decision can be made as to whether more thorough testing is warranted. Recommended screening approaches involve interviews with the patient and a reliable informant, with these interviews being complemented by a short cognitive test that is capable of detecting impaired mental functioning (Table 1). One such test is the Mini-Cog,[7] which combines the Clock Drawing Test (CDT),[8] in which the patient is asked to draw the face of an analog clock displaying a specified time, with a 3-item recall task. The Mini-Cog is a rapid test, requiring only 3 minutes to administer, and it has been shown to be insensitive to potential confounding factors such as language and educational level.[9]

Another instrument that may be used in the rapid screening of patients for AD is the Memory Impairment Screen (MIS),[10] which was designed to improve upon the specificity associated with earlier memory recall tests by incorporating assessments of controlled learning and cued recall capabilities. Patients assessed using the MIS are initially presented with 4 written words and given a verbal category cue for each word. Then, following a 2- to 3-minute nonsemantic delay task, patients are asked to recall the 4 items without the aid of the previously presented category cues, and those cues are subsequently provided only for the items that the patient was unable to retrieve by free recall.

Aside from the Mini-Cog and the MIS, the General Practitioner Assessment of Cognition (GPCOG)[11] has also been recommended for use in the rapid screening of patients for AD. The GPCOG consists of 10 items derived from a total of 3 sources—the Cambridge Cognitive Examination, the Psychogeriatric Assessment Scale, and the Instrumental Activities of Daily Living Scale—and is divided into a 4-item, 9-point cognitive testing section (administered to the patient) and a 6-item, 6-point historical section (administered to a knowledgeable informant). The cognitive testing section is used to assess the patient's ca-

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Table 1. Summary of Brief Cognitive Assessment Tools Used in Alzheimer's Disease Screening Algorithms

Assessment Tool	Test Components	Result(s) Warranting Further Testing	Sensitivity	Specificity
Mini-Cog[7,9]	CDT	Score of 0 on recall task	76%	89%
	3-item recall task (1 point per item)	Score of 1 or 2 on recall task plus abnormal CDT		
MIS[10]	4-item delayed free recall task (2 points per item)	Variable (typically, total score ≤ 5 or ≤ 4)	87%[a]	96%[a]
	Cued recall task for all items not retrieved by free recall (1 point per item)			
GPCOG[11]	4-item cognitive test (maximum score, 9 points)	Score ≤ 4 on cognitive test	85%	86%
	6-item history (acquired from informant; maximum score, 6 points)	Score of 5–8 on cognitive test plus score ≤ 3 on 6-item history		

[a]Sensitivity and specificity rates obtained using 4 as the maximum score warranting further testing.
Abbreviations: CDT = Clock Drawing Test, GPCOG = General Practitioner Assessment of Cognition, MIS = Memory Impairment Screen.

pabilities in the domains of time orientation, visuospatial recognition (as measured by the CDT), and information recall, while the historical section is used to gather information regarding cognitive and functional difficulties that the patient has experienced in the recent past. In addition to possessing high sensitivity and specificity, the GPCOG has been shown to be easy to administer, requiring less than 4 minutes on average for cognitive assessment of patients and less than 2 minutes on average for informant interviews.[11]

Diagnosis

Based on the results of the AD screening evaluation, a decision can be made regarding the need for further testing. Typically, a comprehensive battery of assessments aimed at conclusively confirming or ruling out a diagnosis of AD is recommended for individuals who are identified as having possible cognitive impairment according to one of the rapid screening instruments described above, and also for individuals who, regardless of their cognitive test results, have a history (self-reported or otherwise) of memory difficulties. Strategies for a definitive diagnosis of AD are guided by the criteria described in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR).[12] According to the DSM-IV-TR, AD is characterized by the gradual onset and continuing exacerbation of impairments in learning and memory (relative to previous levels of functioning), with such impairments accompanied by aphasia, apraxia, agnosia, and/or deficits in executive functioning. In addition, the DSM-IV-TR states that the severity of symptoms in AD is such that substantial impairments in social or occupational functioning are seen. A final requirement set forth by the DSM-IV-TR is that other possible causes of dementia—e.g., central nervous system disorders (cerebrovascular disease, Parkinson's disease, Huntington's disease, brain tumor) or systemic conditions (hypothyroidism, vitamin B_{12} or folic acid deficiency, human immunodeficiency virus infection)—be ruled out before a definitive diagnosis of AD is rendered.

History and mental status evaluation. Thorough assessment of patients for the core symptoms of AD begins with the acquisition of a detailed medical history from the patient or from a reliable informant. As part of this acquisition process, it is critical for the clinician to gather information on impairments in cognition and functioning and to determine whether the patient's family history predisposes him or her to the development of dementia. Potential confounding factors, such as the patient's social history (including education, level of literacy, and preferred language) and history of medication use (including prescription, nonprescription, and illegal drugs, as well as herbal agents), should be assessed, as these factors may contribute to an AD-like presentation even in the absence of AD.[6]

Aside from the office history, mental status testing is another necessary component of the diagnostic process, as the confirmed presence of cognitive dysfunction is central to the diagnosis of AD. There are a number of instruments that can assist in evaluating the cognitive status of patients with suspected AD, and current recommendations state that any such instrument that has been widely studied and validated (e.g., the Blessed Information-Memory-Concentration Test,[13] the Blessed Orientation-Memory-Concentration Test,[14] or the Short Test of Mental Status[15]) is appropriate for this purpose.[6] Nonetheless, the Mini-Mental State Examination (MMSE),[16] because it is the most widely used and well-characterized cognitive assessment tool, is generally recommended for confirming the presence or absence of cognitive impairment in patients suspected of having AD. The MMSE, a standardized, 11-item questionnaire used to provide a quantitative measure of cognitive functioning, requires 5 to 10 minutes to complete and does not need to be administered by a psychiatrist. Scores on the MMSE range from 0 to 30, with scores of 21 to 30 being suggestive of normal cognitive functioning or mild impairment, scores of 11 to 20 suggesting moderate dementia, and scores of 10 or lower typically indicating severe dementia.

Despite guidelines detailing the significance of scores on cognitive tests such as the MMSE, it is important to note that cognitive test results should always be interpreted on a case-by-case basis, with consideration given to the tested patient's age, education, and native language. In addition, it should be kept in mind that dementia cannot be diagnosed solely on the basis of cognitive test results and that the results of these tests are but one component of the

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overall clinical picture obtained from a comprehensive assessment procedure.

Neurologic, physical, and psychological evaluation. Another critical issue in the diagnosis of AD is the consideration of other conditions that may cause AD-like cognitive symptoms. For example, a variety of neurologic conditions (e.g., cerebrovascular disease, Parkinson's disease, brain tumor) may lead to the deterioration of learning and memory capabilities even in the absence of AD.[12] Neuroimaging studies can offer useful information for confirming or ruling out a diagnosis of AD. In particular, noncontrast computed tomography (CT) is considered to be a viable option for the ascertainment of neurologic irregularities in any patient with suspected AD, and it is specifically recommended for this purpose in patients younger than age 65 years who show signs of dementia. In addition, among patients 65 years or older with suspected AD, noncontrast CT is recommended for those who have an atypical presentation or for whom diagnosis is otherwise unclear, those who show signs of undiagnosed cerebrovascular disease, and those who exhibit rapid, unexplained cognitive deterioration, unexplained focal neurologic symptoms, or cognitive symptoms showing a temporal relation to a previous head injury.[6] Also potentially useful in the diagnosis of AD is ^{18}F-fluorodeoxyglucose positron emission tomography (PET), a neuroimaging method that was recently declared by the Centers for Medicare & Medicaid Services to be necessary for differentiating AD from frontotemporal dementia in patients who have undergone a thorough clinical workup and satisfy the diagnostic criteria for both of these conditions (i.e., social disinhibition, language difficulties, and impaired executive function).[17]

Aside from neurologic testing, detailed physical assessments are also an essential part of the diagnostic process, as the information obtained from these assessments is critical for ruling out other medical conditions that may cause AD-like symptoms. Patients with cognitive deficits suggestive of AD should be tested for metabolic disorders (e.g., thyroid dysfunction, glucose abnormalities) and nutritional irregularities (e.g., vitamin B_{12} deficiency), both of which may result in AD-like cognitive impairment even when AD is not present. Similarly, because emotional disturbances such as schizophrenia and major depressive disorder may also lead to cognitive dysfunction in the absence of AD, psychological testing is also critical for the differential diagnosis of AD.[18]

Results from the office history, cognitive assessment, and neurologic, physical, and psychological examination should leave the clinician optimally equipped to render a diagnosis of AD if the disease is in fact present in a given patient. Nonetheless, it is inevitable that in some cases the information obtained from these tests will be inconclusive. In such cases, it is recommended that the patient return and undergo the same series of assessments after an interval of 6 months, as additional signs that emerge during that interval may facilitate a more definitive diagnosis.

PHARMACOLOGIC TREATMENT OF AD

Once it has been determined conclusively that a patient has AD, the focus of the clinician must shift to management of the disease. In recent years, pharmacologic treatment options have emerged as potentially valuable contributors to AD management regimens, allowing patients to maintain higher levels of cognition, function, behavior, and quality of life for longer periods of time. However, because a variety of pharmacotherapeutic agents have proven effective in this regard, other factors, such as safety, tolerability, and drug-drug interactions, have emerged as important issues in determining the appropriateness of a particular agent in a given setting.

Safety and Tolerability

Cholinesterase inhibitors. Pharmacologic agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of AD can be divided into 2 classes, with each class having a unique side effect profile. The compounds tacrine (although rarely used), donepezil, rivastigmine, and galantamine fall into the category of therapeutic agents known as cholinesterase inhibitors (ChEIs), which target the symptoms of AD by inhibiting the enzymatic degradation of the neurotransmitter acetylcholine. In doing so, ChEIs increase synaptic acetylcholine levels and thus enhance cholinergic neurotransmission, a process that has been linked to learning and memory. Although ChEI therapy is generally safe and well tolerated, the cholinergic activity of ChEIs may result in the overactivation of central and peripheral acetylcholine receptors, potentially leading to a variety of adverse events.[19] Gastrointestinal side effects are the most common adverse events seen in association with ChEI therapy, as clinical trials involving patients with mild to moderate AD have reported elevated rates of nausea (11%–47%), emesis (10%–31%), diarrhea (5%–19%), and anorexia (4%–17%) in patients receiving ChEIs. Adverse events that occur less commonly, although still more commonly than with placebo, include syncope, muscle cramps, and insomnia. Preliminary evidence suggests that slower dose titration schedules may reduce the likelihood of these side effects, and therefore dose escalation may need to be performed more slowly than recommended in ChEI package inserts.

Memantine. At present, memantine is the lone FDA-approved anti-AD agent that is not an inhibitor of the enzyme cholinesterase. Instead, memantine is classified as a low- to moderate-affinity *N*-methyl-D-aspartate (NMDA) receptor antagonist, deriving its therapeutic efficacy from its ability to block the excitotoxic effects of excessive glutamatergic stimulation while permitting the normal glutamate-mediated neurotransmission necessary for cog-

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nitive processes. Memantine has been shown to be safe and well tolerated in the treatment of AD, exhibiting an adverse event profile similar to or even more favorable than that seen with placebo in a pivotal clinical trial involving patients with moderate to severe AD. In that trial, patients receiving memantine and those receiving placebo showed comparable rates of agitation (18% vs. 32%), insomnia (10% vs. 8%), urinary incontinence (11% vs. 11%), and urinary tract infection (6% vs. 13%), which were among the most common side effects seen in association with memantine therapy. Furthermore, no clinically relevant differences were observed between memantine and placebo in terms of abnormal vital signs, laboratory parameters, or electrocardiographic findings.[20]

Drug-Drug Interactions

Like side effect profiles, drug-drug interactions are a critical consideration in the treatment of patients with AD, particularly because elderly patients are likely to be receiving multiple medications simultaneously. It has been reported that the average elderly person receives 6.5 medications simultaneously—4.5 prescription medications and 2 over-the-counter drugs.[21] In addition, the cognitive dimension of AD further heightens concerns about drug-drug interactions involving antidementia agents, because confusion caused by cognitive impairments may make affected patients more likely to deviate from instructions regarding the safe use of these agents.

Cholinesterase inhibitors. Among the more clinically relevant interactions involving anti-AD agents is the one between ChEIs and atypical antipsychotic agents, as the concomitant administration of drugs in these 2 classes has been linked to parkinsonian symptoms.[22] Parkinsonism is believed to be caused by excessive cholinergic activity in the striatum secondary to diminished dopaminergic neurotransmission. (Dopaminergic neurotransmission suppresses cholinergic signaling.) ChEIs, which enhance cholinergic activity, and atypical antipsychotics, which block dopamine D_2 receptors, are thought to act in complementary fashion to exacerbate imbalances in striatal dopaminergic and cholinergic signaling, with this interaction leading to the appearance or worsening of parkinsonian symptoms in certain patients. Cases of this phenomenon have been reported in patients receiving donepezil concomitantly with an atypical antipsychotic.[23]

With regard to other ChEIs, clinically relevant drug-drug interactions involving galantamine are related to the metabolism of this compound by the hepatic enzyme cytochrome P450 (CYP), and particularly by the CYP2D6 and CYP3A4 isoforms of this enzyme.[22] As a result, compounds that inhibit CYP2D6 and CYP3A4 may interfere with the metabolic breakdown of galantamine, leading to supranormal plasma concentrations and potentially more severe side effects. In fact, pharmacokinetic studies have demonstrated that the bioavailability of galantamine increases by an average of 12% with concomitant administration of the antibiotic erythromycin, which inhibits CYP3A4, and by an average of 30% when the antifungal agent ketoconazole, which also inhibits CYP3A4, is administered concomitantly. Likewise, concomitant administration of the antidepressant paroxetine, a known inhibitor of CYP2D6, has been linked to an increase of 40% in the bioavailability of galantamine.[24]

Clinically relevant interactions mediated by hepatic enzyme pathways appear to be less of a concern with ChEIs other than galantamine.[22] For example, pharmacokinetic studies have shown that donepezil, although similar to galantamine in that it is metabolized primarily by CYP2D6 and CYP3A4, does not appear to have its bioavailability significantly increased by inhibitors of these isoforms. Similarly, because rivastigmine, the other commonly used ChEI, is metabolized primarily by cholinesterases rather than members of the CYP family, pharmacokinetic drug-drug interactions involving this compound are unlikely as well.

Memantine. The NMDA receptor antagonist memantine carries a minimal likelihood of drug-drug interactions, as this compound does not significantly induce or inhibit hepatic enzymes and remains relatively unchanged by metabolic processes as it passes through the body.[25] Given recent interest in the use of combination therapy regimens involving memantine and ChEIs due to their complementary mechanisms of action in attenuating the symptoms of AD, the preliminary finding that memantine does not affect the activity of ChEIs in vitro is particularly noteworthy. Another encouraging finding is that combination therapy with stable doses of memantine and a ChEI (modal memantine dose, 20 mg/day; N = 72) resulted in no serious adverse events over the course of a 4-month postmarketing surveillance study, with treatment being well tolerated by 98% of the 158 participants in that study.[26] Memantine is not completely devoid of potential drug-drug interactions, however, as memantine clearance has been shown to decrease by approximately 80% when urine is basic (pH ~8.0) rather than acidic.[27] Thus, agents that alkalinize urine (e.g., carbonic anhydrase inhibitors, which are used in the treatment of glaucoma) may result in suboptimal clearance, leading to abnormally high levels of memantine in plasma.

Assessment of Therapeutic Efficacy

If, after weighing the risks and benefits associated with the available options, the decision is made to treat AD using a pharmacologic agent, a systematic approach to monitoring therapeutic efficacy can be implemented. Upon reaching the maximal tolerated treatment dosage for a given patient (by following the specified dose titration guidelines for the agent of choice), cognition, functioning, and behavior should be assessed, with the resulting findings serving as a set of baseline measurements. Then, following this baseline evaluation, cognition, functioning, and

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behavior should be reevaluated once every 3 to 6 months, along with treatment compliance and side effects, to determine whether the benefits of therapy outweigh any negative consequences that might arise.[6]

THE CAREGIVER IN AD

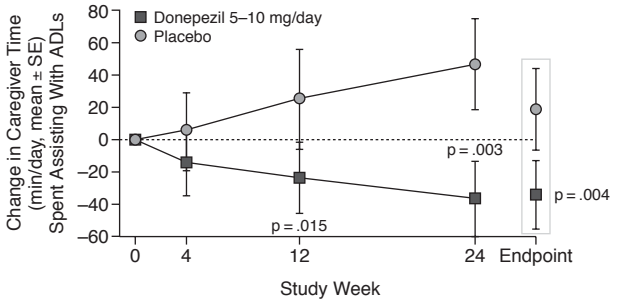
The impact of AD is not limited to the affected patient, as the disease can have substantial negative effects on the emotional, physical, and financial well-being of the patient's primary caregiver as well. Alzheimer's disease caregivers report poorer self-rated health, increased depressive symptoms, and more use of psychoactive medications relative to control individuals or to the age-matched general population,[28,29] and the magnitude of the caregiver burden increases as the disease progresses.[30]

The AD-related burden and diminished quality of life experienced by the caregiver may have a negative impact on the affected patient as well. A 12-month study involving 181 Spanish caregivers found that caregiver quality of life (measured using the Short Form Health Survey) was inversely correlated with the likelihood of nursing home placement of the care recipient.[31] In that study, dramatic decreases in caregiver quality of life between baseline and endpoint were linked to a 6.4-fold increase in risk of institutionalization over the course of the study.[31] Furthermore, another trial involving 206 caregivers—all spouses of patients with AD—found that patients whose caregivers were randomized to undergo 6 counseling sessions and join an AD caregiver support group had their nursing home placement delayed by a median interval of 329 days relative to patients whose caregivers were not required to receive counseling or join a support group (p = .02).[32]

Given the importance of caregiver well-being for both caregiver and patient, it is clear that optimal strategies for the management of AD should explicitly take into account the welfare of the care provider. Thus, it is critical for the clinician to ensure that patient-focused interventions be accompanied by interventions that target the caregiver. As a first step upon diagnosis of AD, information should be provided regarding the various avenues through which caregivers may obtain emotional support and practical assistance. For example, caregivers should receive an overview of community organizations that offer relevant counseling and educational services, and they should also be made aware of available adult day care and respite care programs, which provide temporary care for patients with AD and thus afford care providers a short break from their caregiving duties. Furthermore, throughout the course of the disease, the clinician should regularly inquire about the levels of burden and stress experienced by the caregiver, who may otherwise be reluctant to express concerns regarding his or her own well-being.

Educational efforts aimed at providing detailed information on the natural course of AD represent another important facet of caregiver management. Such efforts help to establish more concrete expectations for the caregiver, thereby alleviating any fear of the unknown that the caregiver might be experiencing. Furthermore, educational interventions of this type, when coupled with efforts to educate the caregiver regarding available AD treatment options, can reduce caregiver stress by facilitating the development of a comprehensive plan for patient care throughout the various stages of the disease.

Figure 2. Changes in Caregiver Time Burden Over the Course of a 24-week, Randomized, Double-Blind, Placebo-Controlled Trial of Donepezil for Patients With Moderate to Severe Alzheimer's Disease[a]



[a]Data from Feldman et al.[33]
Abbreviations: ADLs = activities of daily living, SE = standard error.

As an adjunct to these nonpharmacologic, caregiver-targeted interventions, pharmacologic treatment of patients with AD may result in favorable caregiver outcomes. For instance, in a 24-week, randomized, double-blind, placebo-controlled trial involving 290 patients with moderate to severe AD (baseline MMSE range, 5–17), donepezil monotherapy (N = 111), when compared with placebo (N = 110), was found to reduce the amount of time that caregivers spent assisting their patients with ADLs by 52.4 min/day (p = .004; Figure 2).[33] Similar findings were made in a pooled analysis of 2 concurrent 6-month, multicenter trials in which a total of 825 patients with mild to moderate AD (baseline MMSE range, 11–24) were randomized to receive placebo or galantamine monotherapy at the recommended dosage of 24 mg/day.[34] In that analysis, caregivers of galantamine-treated patients (N = 411) were found to spend an average of 32 min/day less assisting with ADLs when compared with caregivers of placebo-treated patients (N = 414) at study endpoint (p = .011).

The observation of caregiver benefit in association with AD pharmacotherapy is not limited to ChEIs, as evidenced by the results of a 28-week trial in which 252 patients with moderate to severe AD (baseline MMSE range, 3–14) were randomized to receive either memantine 20 mg/day or placebo.[35] An analysis of the trial's treated-per-protocol population revealed that, by 28 weeks, caregivers

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of memantine-treated patients (N = 97) were spending significantly less time (104 min/day; p = .02) assisting with ADLs than were caregivers of placebo-treated patients (N = 84). Furthermore, similar findings were made in a last-observation-carried-forward analysis of the corresponding intent-to-treat population (mean difference between memantine [N = 126] and placebo [N = 126], 92 min/day; p = .01).

SUMMARY

Although AD has profound negative consequences for patients and their caregivers, strategies do exist for minimizing the burden of this disease. However, patients with AD cannot benefit from these strategies unless their condition is properly identified, and so prompt and accurate diagnosis of AD is of primary importance. Once the presence of AD has been recognized in a patient, attention can be directed toward the development of a suitable approach to disease management. Pharmacologic interventions may play an important role in such approaches, as a variety of agents have been shown to effectively slow the progression of AD-related symptoms and reduce caregiver burden. Nonetheless, decisions regarding pharmacotherapy should take into account the specific needs of each patient and the way in which these needs balance with the unique efficacy, safety, and tolerability profiles associated with the agents being considered for use.

Drug names: donepezil (Aricept), erythromycin (Eryc, E-glades, and others), galantamine (Razadyne), ketoconazole (Ketozole and others), memantine (Namenda), paroxetine (Paxil, Pexeva, and others), rivastigmine (Exelon), tacrine (Cognex).

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