Management of Alzheimer’s Disease

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ALZHEIMER’S disease (AD) is a devastating and debilitating neurodegenerative condition and the most common cause of dementia in the elderly. AD may not be a single disease but rather a group of diseases with overlapping pathogenic mechanisms and clinical manifestations. The condition accounts for an estimated 60–70% of all dementia disorders in the elderly (1). Between 5% and 10% of the population aged 65 years and older, and up to 50% of those older than 85 years of age, are estimated to suffer from AD (2). One hundred thousand deaths per year are attributed to AD in the United States. In the last 50 years, AD has grown from relative obscurity to becoming a defining characteristic of industrialized society. In 1950, at the most 200,000 people in the United States suffered from the ailment. The total stands at 4 million today (3). By 2050, barring a cure, the number of U.S. sufferers is expected to reach 16 million, out of a total of 80 million sufferers worldwide (4).

Despite consensus on both clinical (5) and neuropsychological (6) definitions of AD, only limited information is known about its etiology and pathogenesis. It is probably caused by several mechanisms that include both genetic and environmental influences (7). The disease manifests as a relentless decline in a broad range of intellectual and functional abilities, followed eventually by death. In addition, as many as 90% of people with AD demonstrate clinically significant behavioral and psychological symptoms at some point in the course of the illness, causing severe emotional suffering. Caring for patients with AD imposes an immense burden on caregivers (8).

Although most patients with AD develop the disease after the age of 65, 5–10% develop the disease at a younger age (early-onset AD). Less than 10% of patients with AD, almost all being early-onset AD, have a familial AD with an autosomal dominant pattern of inheritance. Abnormal genes on chromosomes 21, 14, and 1 appear to account for the vast majority of cases of the early-onset familial AD (9–11). All these genes are almost fully penetrant.

There are 3 stages of AD—mild, moderate, and severe—with cognitive and functional decline stretching over 5–8 years on an average (range 2–20 years) (Table 1) (12). A recent study indicates that people with AD often die within about 3 years of diagnosis, especially those above the age of 85—a far grimmer prognosis than was previously thought to exist (13). Without treatment, the initial, mild stage usually lasts 2–3 years, during which time patients show short-term memory impairment, often accompanied by symptoms of anxiety and depression. During the moderate stage these symptoms appear to abate, as neuropsychiatric manifestations such as visual hallucinations, delusions, and reversal of sleep patterns emerge. The severe and final stage is characterized by motor signs such as motor rigidity and prominent cognitive decline. Cognitive and functional decline tend to be linear throughout the 3 stages of the disease, whereas caregiver burden is high in severe AD, since at this point patients require almost total care; the physical care burden is the greatest, although the neuropsychiatric care burden can also be considerable.

MANAGEMENT OF AD

Although the focus of many physicians is the management of AD with cholinesterase inhibitors (ChEI), it is crucial that physicians develop a global management strategy for their patients with AD and their caregivers. Global management includes early accurate diagnosis and providing counseling and pharmacological treatment to the patient and the family/caregiver (Table 2). The patient and family must agree with the physician on the treatment ultimately selected for use; this decision must include duration and cost considerations. Both the patient’s premorbid functioning and potential impact on their quality of life must be taken into account when making any treatment decisions for AD patients. A thorough evaluation of comorbid medical and psychiatric disorders and a review of current medications (including discontinue medication unnecessary or harmful medications) are important. As over-the-counter products are popular, physicians are encouraged to ask about their use and to provide appropriate counseling regarding their safety and efficacy. During the evaluation phase, emphasis must be placed on establishing a good rapport with the patients and their families. Regularly scheduled visits, every 1–2 months initially and then every 3 months, for health maintenance and routine patient assessment will assist in maximizing independence and functioning and will minimize behavioral disturbances associated with the progression of the disease. Families with early-onset familial AD may be encouraged to enroll in a research database for potential future curative therapies.

Naming the Disease

The management of AD begins with naming the disease and evaluating its severity. The clinical diagnosis of AD can be accurate 90% of the time. Recent data indicates that AD can be accurately diagnosed even in very mildly impaired individuals (14). A definitive diagnosis of AD still can be
Role of the Primary Care Physician

The primary care physician will manage a growing number of persons with AD and their family members or other caregivers upon whom these patients depend. In addition to the diagnostic and pharmacologic treatment components of managing AD, the physician will be called upon to assist with the behavioral, social, economic, legal, and living-environment problems facing the patient and her or his family. A team approach to managing these complex problems of AD is a practical and effective management strategy. In addition to nurses and physician assistants, the team may include those with expertise in neurology, geriatric psychiatry, social work, clinical psychology, and elder law. The neurologist assists in the differential diagnosis of patients with atypical dementia presentation and in the management of later stage neurologic features of AD, such as seizures. The geriatric psychiatrist assists in the differential diagnosis of complex cases and in the recognition and psychopharmacologic management of behavioral problems such as agitation, psychosis, and depression. The social worker assists in maintaining the integrity of the patient’s family unit and in identifying and mobilizing community care resources and may provide psychotherapy for patients and caregivers. The clinical psychologist assists in the diagnosis of early-stage or questionable dementia and provides expertise in behavioral approaches to such problems as depression. The elder law attorney assists in addressing issues such as guardianship and health-care financial planning. Experts from other disciplines such as pharmacy, nutrition, physical therapy, and occupational therapy can also make important contributions to management. For patients with early-onset familial AD, referral to a geneticist or a genetic counselor for the whole family and the patient is recommended.

Educating the Patient and Caregiver

During the workup and in disclosing the diagnosis to the patient and the family, the clinician begins to educate about AD. This discussion should include a frank, honest, balanced view of what is known about the disease process and available treatment options. Education regarding the recognition of current symptoms and the symptoms likely to occur with progression of the disease will assist in formulating plans for safety and health maintenance. Additional sources of education should be provided. These may include material written for the lay person, such as The 36-Hour Day (16) and Forget Me Not (17). The 3 ‘‘R’S’’—repeat, reassure, and redirect—can help caregivers reduce escalating behaviors and limit the need for pharmacologic management. Caregivers should be counseled to help patients with AD maintain social and intellectual activities as tolerated, especially important family events.

Referrals to local and national groups, such as the Alzheimer’s Association, that are dedicated to the education and support of patients with AD is strongly recommended. Information about agencies such as the Administration on Aging (202-619-1006), the Alzheimer’s Association (800-272-3900, www.alz.org), the Alzheimer Research Forum (www.alzforum.org), and the Alzheimer’s Disease Education and Referral Center (800-438-4380, www.alz.org) should be provided. An additional resource may be the American Bar Association Commission on Legal Problems of the Elderly (202-662-8690). Other community services, such as the local chapters of the Agency on Aging, Meals on Wheels, and organizations providing transportation, may all be important as a means of reducing the burden of care-

<table>
<thead>
<tr>
<th>Stage</th>
<th>Duration (years)</th>
<th>Global Deterioration Scale (score)*</th>
<th>Mini-Mental State Exam (score)†</th>
<th>Global Autonomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>2–3</td>
<td>3–4</td>
<td>26–18</td>
<td>Independent living</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>5</td>
<td>17–10</td>
<td>Supervision required</td>
</tr>
<tr>
<td>Severe</td>
<td>2–3</td>
<td>6–7</td>
<td>9–0</td>
<td>Total dependence</td>
</tr>
</tbody>
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* Scale measures progressive need for assistance in daily activities (e.g., choosing clothes, dressing); scores range from 1–2 (normal) through 6–7 (severe dysfunction (219).  
† This 22-item scale measures cognitive function; scores range from 30 (excellent function) to 0 (severe dysfunction) (220).

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giving. The physician is the critical conduit for providing this information to the caregiver.

Genetic Testing

Testing for the apolipoprotein E-4 (APOE-4) gene, one form of a gene on chromosome 19 that is more common in individuals with AD than in age-matched individuals without dementia, is not currently recommended for use in diagnosis because it is found in many undemented elderly and is not found in many patients with AD (18,19). Empirical data on the benefits and potential harm of genetic susceptibility testing with APOE-4 are currently being collected and studied in the multicenter REVEAL study (Risk Evaluation and Education for Alzheimer’s Disease) (20). Patients with early-onset familial AD should be referred to Alzheimer Disease Research Centers for counseling regarding the potential benefits of genetic testing. An impersonal relationship or an encounter created solely for the purpose of risk assessment would seem more vulnerable to miscommunication than would an encounter discussing risk assessment that is embedded in a long-term clinical relationship (20).

Caring for the Caregiver

Caring for the caregiver is an essential element of managing the patient with AD. The majority of patients with AD are cared for by family members or other caregivers in their own homes. They frequently continue to devote a substantial amount of time to caring for a patient after admission to a nursing home. Caregivers are responsible for administering medication prescribed by the physician. The burden of caregiving exacts a heavy toll: it is estimated that about half of all caregivers of people with dementia suffer severe emotional distress, and dementia caregivers have significantly higher rates of depression, physical illness, and other health-related problems (21,22). Almost 90% of caregivers interviewed in one study reported fatigue, anger, and depression directly linked to caring for a demented family member (23). Fatigue is probably the most underestimated reaction. Caregiving is also associated with a greater use of sedative hypnotics and a higher mortality rate among caregivers. Caregivers must be warned of the dangers of emotionally, physically, and financially depleting themselves, and regular assessments must be made to screen for psychiatric disorders in the caregivers. Spouses of patients with AD should be also screened for a dementing illness if, during the patient’s evaluation, the physician learns about cognitive impairment in the spouse. Caregivers often do not recognize that their guilty feelings lead them to make unrealistic demands. It also is not uncommon for spouses or children to feel that they would be betraying their relatives by sending them to a nursing home.

Many caregivers are reluctant to ask for help. It is important that health care providers ask the caregivers if they need assistance and validate their feelings. Clinicians must be prepared to help the caregivers deal with anger, denial, anxiety, guilt, grief, and clinical depression as they adjust to the progression of the disease. The grief and adjustment process for a caregiver is complex and cyclical, potentially reactivated by the additional impairments at each new stage of the illness. Family and caregiver interventions will help not only the caregivers but also the patients with AD by preventing premature institutionalization (24,25). Educational program, training program, support, and respite services directed toward caregivers of dementia patients may improve their coping skills and reduce stress (26–29).

Reducing Excess Disability/Functional Impairment

Many factors contribute to functional impairment in patients with AD. They include social issues, cultural expectations, environmental factors, sensory deficits (hearing and vision), pain, coexisting disease states (e.g., over-correction of hypothyroidism, vitamin B12 deficiency, etc.), fear of falling, and lack of motivation. Treatment of medical comorbidity can improve function (30) and can be important in delaying the progression of frailty (31). For patients who need them, the value of new eyeglasses or a hearing aid cannot be overemphasized. Such devices facilitate patients’ understanding of and participation in the choices surrounding care at the end of their lives. Addressing these issues can greatly improve AD patients’ functional and even cognitive abilities. In addition, nursing care and care by caregivers that creates dependency is a significant factor in causing excess functional impairment. Teaching the caregivers (at home as well as in long-term care facilities [LTCFs]) to implement a restorative philosophy of care is recommended. Restorative care focuses on the restoration and/or maintenance of physical function and helps AD patients to compensate for functional impairment so that the highest level of function is obtained.

Counseling Regarding Specific Issues

Should the Patients Be Told of Their Diagnosis?

In sharing the diagnosis of dementia, one needs to consider each patient individually (32). Generally speaking, patients in their early stages need to know the nature and prognosis of their disease once the diagnosis is clear to the treating physician. Physicians must not allow their own discomfort—or the misguided requests of family members—to subvert the honesty with which they relate to patients. It is also important to ensure that the patient’s ability to comprehend is at its highest possible level. Disclosure may also assist in persuading the patient to accept help and in managing social needs (33). It also enables the issue of driving safety to be addressed. With the development of new drug treatments, disclosure allows patients to consent to participation in clinical trials when they still have the capacity to consent. Currently most research relies on relatives to give proxy consent, although this has been challenged as legally unacceptable (34). This said, there are circumstances in which it may be ill-advised to tell a patient that he/she has AD during the first few visits. For example, if the patient has no support system, there is a potential that such a disclosure may undermine his will to live. In such situations, it may be prudent to first assist the patient in establishing support networks and relevant services and then sensitively disclose the diagnosis.

In the late stages of disease the truth may neither benefit nor harm the patient (33). Of course, there exists a greater
dilemma in the cases in which some patient understanding remains. With sensitivity, flexibility, and discretion, such bad news may still be delivered. Disclosure of diagnosis should not be a one-office-visit event and must be seen as an ongoing, dynamic process and a fundamental part of the care of a patient with dementia.

Discussion of Future Financial, Health Care, and End-of-Life Issues

Physicians should help both the family and patient to establish medical and legal advance directives for patients with AD and should recommend updating the patient’s will early in the course of treatment (35). Open discussions regarding role and responsibility changes within the family system should be encouraged. Assignment of health care proxy, durable power of attorney, and discussion of end-of-life issues, including living wills, should be addressed while the patient is competent to make informed decisions regarding these concerns. It is important to introduce the topic of advance directives sooner rather than later. The unpredictability of serious events such as hip fracture, pneumonia, etc., drive home the point that the discussion should take place before the crisis occurs. Discussions about advance planning do not have to be lengthy or conclusive. But the topic should be an agenda item in encounters with patients with dementia, much like nutrition and safety are.

Safety Issues

Clinicians should counsel the caregivers regarding various safety issues in the home. Caregivers need to be told when the patient will start needing 24-hour care and supervision.

Driving.—Many elderly patients with AD may continue to drive despite having impaired abilities (36–38). Physicians often fail to identify signs of impaired mental performance in their older patients, further compounding this issue. A history of getting lost, misjudging distances, inappropriate speed, missing signs or signals, moving violations, motor vehicular accidents or near misses, passenger panic, etc., should be documented (39,40). A substantial proportion of even mildly demented people are not safe drivers when directly observed. A substantial proportion of mildly demented people can pass performance tests. For patients with very mild AD, formal, serial performance evaluations are recommended. Patients with more advanced AD should be recommended to discontinue driving. All patients with AD should be systematically evaluated regarding their driving abilities.

Presence of firearms.—Many elderly in the United States have firearms in their households, most of which are stored loaded (41). Each patient and his or her family/caregiver must be specifically asked about access to firearms. The physician must advocate for the safe storage or removal of these firearms. Any firearms in the patient’s house should be disabled in order to prevent accidental gunshot wounds or deaths.

Wandering.—Families should be warned of the hazards of wandering. Supervised walks and using door locks or electronic guards to prevent wandering are recommended. Registration with the Safe Return Program through the Alzheimer’s Association should be encouraged. Ethical considerations should be kept in mind when using electronic tagging devices in patients with AD who have a tendency to wander (42). When used, particularly in mild AD patients, these devices are often demoralizing and dehumanizing.

Poisonous or harmful substances.—Families and caregivers need to be counseled to keep such substances out of the reach of patients with AD.

Other safety concerns.—Families and caregivers should be counseled to modify the place of living in order to reduce objects and hurdles that might increase the risk of falls. Sharp objects should be kept out of the patient’s reach, and appliances and power tools should be kept unplugged and out of sight. Smoke alarms should be kept in working order. A home visit for safety assessment and guidance by a social worker may be helpful.

Counseling Regarding Long-Term Care Placement

As many as 90% of patients with AD reportedly become institutionalized before death (43). However, most patients with AD continue to live in the community until family caregivers are no longer able to care for them. Patient characteristics (e.g., high cognitive impairment, one or more dependencies in ADL, difficult behaviors) and caregiver characteristics (e.g., high caregiver burden) are both important determinants of long-term care placement for patients with dementia (44). Planned admissions to a LTCF may be better than unplanned admissions (45). Numerous local, state, and federal agencies monitor nursing homes, but vigilant, assertive family members may be most helpful in assuring quality care. High-quality LTCFs encourage family participation. Before choosing a LTCF, consumers should examine reports of the deficiencies found in state inspections. These can be accessed at the website www.medicare.gov. Family members should also contact their state Department of Health with concerns about general conditions or care in nursing homes; the ombudsman in their local aging department about problems with finances, property, or other consumer concerns; and local police or their aging department’s office of protective services with any concerns about abuse.

Other Important Issues

Abuse and Neglect

Patients with AD are certainly at high risk of abuse and neglect (46). Estimates of the prevalence of abuse of older adults suffering from dementia range from 5.4% to 11.9% (46). They far exceed the 1–4% prevalence rates typically cited for all older adults, cognitively intact as well as demented (47). The physician must acknowledge that not only will some family members have conflicts with AD patients, but a small number will actually neglect or abuse their AD relatives. This also applies to nonfamily members or professional caregivers. Physicians must be able to identify the
potential for emotional, physical, sexual, and financial abuse or neglect, detect its occurrence, and deal with situations in which abuse is present. Financial abuse by telemarketers and other people (including those on television) who make patients with AD easy victims of solicitation should also be suspected and reported to the state’s attorney general office. A prior history of abuse is associated with a greater likelihood of abusiveness once dementia occurs. Malnutrition, noncompliance with medications, bruises, decubiti, poor personal hygiene, and other evidence of trauma are some of the signs that should alert physicians that abuse or neglect may be an issue. Physicians need to learn their state’s law on reporting of suspected elder abuse. Interventions such as supportive counseling, individual or family psychotherapy for caregivers, respite or in-home care services for patients, and alternative living situations for all parties concerned may be helpful.

End-of-Life Care

Dementia severity and other patient characteristics are important for informed end-of-life decision making and for assessing effectiveness of interventions in severely demented patients in order to prevent an unfavorable outcome of medical comorbidity, such as pneumonia or hip fracture (48). Patients with advanced dementia commonly develop difficulty eating, often when they become bedridden and dependent in all activities of daily living (49–51). They may resist or be indifferent to food or fail to manage the food bolus properly once it is in the mouth (oral phase dysphagia). In moderately demented patients, prevention of aspiration and weight loss, if possible, may improve midterm outcome (52). Enteral tube feeding is intended to prevent aspiration pneumonia, to forestall malnutrition and its sequelae, including death by starvation, and to provide comfort. There is no evidence to indicate that tube feeding improves any of these clinically important outcomes, and some data seem to indicate that it does not (53,54). Indeed, tube feeding may increase the risk of aspiration. In addition, the risks of this treatment are substantial. Nasogastric tubes may promote sinus and middle ear infections, and gastrostomy tubes may cause cellulitis, abscesses, necrotizing fasciitis, and myositis. Many patients are put in physical restraints to prevent tube removal. For severely demented patients, the practice of tube feeding should be discouraged on clinical grounds, but this decision needs to be made in the context of the patients’ and families’ moral and religious belief systems. There are no published studies that compare tube feeding to oral feeding.

It is possible to convert tube feeding to hand feeding and, in some cases, patients may be able to feed themselves again (55). Withdrawing sedatives and psychotropic medications should be considered in AD patients with swallowing problems, because these medications may reduce consciousness and thus predispose the patient to aspiration pneumonia. Improving oral care is recommended to reduce oropharyngeal colonization by pathogens. Inadequate staffing and lack of supervision at mealtime may contribute to weight loss in nursing homes. If fed quickly, AD patients may cough or choke or aspirate. Adequate staffing and allowing patients with AD to take their time to eat is thus very important.

In the presence of dementia, successful cardiopulmonary resuscitation (CPR) is 3 times less likely to succeed, as compared to CPR in patients with metastatic cancer (56). In addition, in the demented population, most cardiac arrests occur in long-term care institutions, not acute-care hospitals. The success rate of CPR is only 1% in demented LTCF residents. The benefits of successful CPR are further diminished because of injuries, such as broken ribs, associated with CPR and because of the need for mechanical ventilation. Families should be counseled about these outcomes and whether the patient and family would like “do not resuscitate” directives instituted. These discussions should ideally occur when the patient is in the early stages of AD and thus can be an active participant.

Antibiotic therapy may be withheld in some frail AD patients who are expected to die soon (such as patients in their severe to terminal stages of AD). Most severely demented AD patients are indeed frail and at high risk of dying from pneumonia or sepsis, in spite of antibiotic treatment (54). Palliative management of symptoms such as pain, dyspnea, etc., in patients with severe to end-stage AD should be similar to that used in patients who are dying from cancer. An agreed-upon, documented goal and treatment approach for all health-care team members is an essential component of end-of-life care for AD patients. Management should involve vigilance to ensure good symptom management, support to families of patients with AD in their end-stages of dementia, communication with other health team members, and objective documentation. Palliative care is an appropriate treatment strategy for the management of patients with advanced AD. Palliative care should never mean that the patient with AD receives less care. Rather, palliative care replaces aggressive intervention, with care oriented toward comfort. Hospice care may be appropriate for patients with AD in the terminal stages of the disease (57).

Pharmacotherapy of AD

ChEI Therapy

This class of drugs is presently regarded as the standard treatment of AD. Four ChEIs have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of mild to moderate AD. They are tacrine, donepezil, rivastigmine, and galantamine. These compounds increase the concentration of acetylcholine and the duration of its action in synapses by inhibiting the degradation of acetylcholine. These compounds provide symptomatic treatments and may also have disease-modifying effects. They have been shown in several large, multicenter, randomized, double-blind, placebo-controlled trials (of 3–6 months’ duration) to improve cognitive function, global outcome, and activities of daily living (58–61). There is also accumulating evidence that ChEIs may improve behavioral and psychological symptoms of AD, such as psychosis and apathy (62). Treatment with ChEIs may also help caregivers by reducing the burden of caregiving (63). The mean effect of drug over placebo represents an improvement in cognition roughly equivalent to stemming 6–12 months of natural decline in untreated patients. There is preliminary evidence from a retro-
spective return drop-out data indicating that the effects of rivastigmine on cognition may be sustained in rivastigmine-treated patients and indicating that rivastigmine may affect disease progression (64). Evidence with the ChEIs also suggests that the effect is extremely variable, with large improvements in some patients and none in others. At the moment we have no reliable way of distinguishing potential responders from nonresponders. When response occurs, it does so relatively quickly (12 weeks). The only certain way of proceeding is therefore to use a ChEI for at least 12 weeks at the proper dose and to observe the results systematically. The physician should seek evidence of changes in all 3 domains (cognition, ability to perform ADL, and behavior) to determine if the patient has benefited from the ChEI. Group means hide a marked heterogeneity of response, as 40–50% of patients show a definite clinical improvement (≥4 points on the AD assessment scale–cognitive subscale [ADAS-cog], equivalent to stemming half a year or more of natural cognitive decline), whereas 20% show a stronger response (≥7 points on the ADAS-cog, equivalent to stemming a year or more of natural cognitive decline). Responders are maintained close to baseline for 12–18 months on both cognitive and noncognitive measures. No reliable predictors of response have emerged, and in each patient, careful assessment of benefit needs to be undertaken after 2–4 months of treatment.

Tacrine.—Tacrine was the first ChEI to be approved specifically for the symptomatic treatment of patients with mild to moderate AD. The starting dose for tacrine is 10 mg 4 times daily, and this dose is increased by 40 mg/day no more frequently than every 4 weeks (according to tolerance), to a maximum daily dose of 160 mg (40 mg 4 times daily). Tacrine has been associated with hepatotoxicity (65) and thus requires baseline and multiple follow-up liver enzyme determinations. This along with the need for multiple daily dosing makes it unsuitable as a ChEI of first choice. We recommend that its use be restricted to patients who do not tolerate or respond to ChEIs. Tacrine is extensively metabolized by the liver via the cytochrome P450 1A2 isoenzyme system; therefore, it has the potential to interact with other medications metabolized by this isoenzyme, such as theophylline, fluvoxamine, and cimetidine. Tacrine should be avoided in patients with liver disease.

Donepezil.—Donepezil was the second ChEI approved by the FDA for symptomatic treatment of mild to moderate AD in the United States. Two placebo-controlled clinical trials of donepezil have been reported in which efficacy was demonstrated for 1 year in mild-to-moderate AD based on cognitive (66) and functional (67) measures. Donepezil is largely metabolized by the liver, although some of the dose is recovered in the urine as unchanged drug (11–17%) (68). It is metabolized by the cytochrome P450 isoenzymes 2D6 and 3A4. Clinically relevant drug interactions with other drugs have not been studied. Interaction with paroxetine (patient developing increased confusion and agitation) has been reported (69). Caution should be exercised in using donepezil in patients with severe hepatic or renal disease. The recommended starting dose is 5 mg daily, which is increased to 10 mg daily after 4–6 weeks. Morning dosing of donepezil may be preferable in some patients who experience nightmares or insomnia. It may be taken without regard to meals unless gastrointestinal side effects occur, in which case it should be taken with meals. Although there is 1 case report of fulminant hepatitis with the concomitant use of donepezil and sertraline (70), laboratory monitoring of liver enzymes is not required.

Rivastigmine.—This was the third ChEI approved by the FDA for symptomatic treatment of mild to moderate AD in the United States. Rivastigmine should be titrated every 4 weeks, as opposed to every 2 weeks, as recommended when the drug was first made available. Slower titration and taking rivastigmine with a full meal significantly improves tolerability, especially with regard to gastrointestinal side effects. One unique feature of rivastigmine that distinguishes it from other ChEIs is the very low risk of drug interactions in AD patients receiving multiple medications for “real-world” comorbidities (71). This is because the metabolism of rivastigmine occurs primarily via enzymatic cleavage (hydrolysis) by cholinesterases at the site of action and does not require the cytochrome P450 enzyme system. The starting dose is 1.5 mg twice a day with meals (breakfast and supper), and this dose is increased by 3 mg/day, not faster than every 4 weeks (as tolerated), to a therapeutic dose of 6–12 mg/day. The highest tolerated dose is recommended, as there is some evidence that higher doses may provide greater benefits. A more rapid progression of AD while receiving placebo treatment was predictive of a significantly stronger patient response to rivastigmine therapy on various measures (72). Laboratory monitoring is not required.

Galantamine.—This was the fourth ChEI approved by the FDA for symptomatic treatment of mild to moderate AD in the United States. Metabolism is hepatic via glucuronidation and the cytochrome P450 isoenzymes 2D6 and 3A4; interactions with other drugs that are metabolized through this pathway are therefore possible. Caution should be used in patients with liver disease. The starting dose is 4 mg twice a day, and this dose is increased every 4 weeks. The therapeutic dose is 16–24 mg/day. A 6-month study showed no additional benefit and a higher rate of side effects with a dose of 32 mg/day (73). Laboratory monitoring is not required.

Role of Butyrylcholinesterase and Nicotinic Modulation

Humans have 2 types of cholinesterase: acetyl and butyryl. The physiological role of butyrylcholinesterase is being investigated, but levels of this enzyme have been shown to increase as AD progresses, whereas levels of acetylcholinesterase decrease (74). Both enzymes are found in neuritic plaques, and their inhibition with ChEIs may modify the deposition of beta-amyloid, a key component of the pathophysiology of AD as we currently understand it. The clinical significance of this action, if any, in terms of slowing progression of the disease or better symptomatic efficacy in later stages has yet to be fully established. Of the currently available ChEIs, only tacrine and rivastigmine have the ability to inhibit butyrylcholinesterase. Of the currently avail-
able ChEIs, only galantamine has the property of allosteric modulation of the presynaptic nicotinic receptors. The potential significance of this effect is additional increase in cholinergic neurotransmission. Whether this provides any additional clinical benefit over other ChEIs has not been proved at the present time.

Which ChEI Should Be the First Choice?

Only direct comparisons between various currently available ChEIs will provide definitive data that can be used to maximize patient outcome. In general, these agents all have similar degrees of efficacy. However, there are some important differences (refer to Table 3). Certain patients may benefit more from one particular agent over the others. For AD patients living alone who do not have close daily supervision over their medications, donepezil may be preferable because of its once-a-day dosing. For patients with AD who also have hepatic disease or who are on numerous other medications metabolized by cytochrome P450 2D6 and 3A4 enzymes, rivastigmine may be preferable because of its lack of cytochrome P450 metabolism. Patients with AD who experience impaired sleep or excessive dreaming with donepezil may benefit more from rivastigmine or galantamine.

Switching From One ChEI to Another

There is some preliminary evidence that if a patient does not respond to one ChEI, switching to another may be beneficial (75,76). Switches can also be performed to cope with side effects (75,77). In general it is not difficult to switch from one drug to another among the 3 ChEIs (donepezil, rivastigmine, and galantamine). Combination of ChEI is not recommended. Standard dose escalation using monthly titration is recommended. Preliminary data indicate that for patients experiencing no safety/tolerability problems on a ChEI, another ChEI can be administered the following day with no washout period (78,79). If the patient is experiencing safety/tolerability problems with a ChEI, a washout period of 7 days, or until symptoms resolve, is recommended before switching to another ChEI (78,79). As yet, no guidelines for switching from one ChEI to another have been published.

Importance of Starting ChEI Early

Patients with AD who begin treatment with a ChEI later do not do as well as those who began treatment early (73,80,81). In a 1-year study, in which the double-blind, placebo-controlled phase lasted for 26 weeks, all subjects—whether started on rivastigmine or placebo—were switched to open-label rivastigmine and followed for an additional 26 weeks (81). Patients who were initially placed on placebo and later started on rivastigmine seemed to respond to the ChEI and had a significant increase in cognitive function, but then they started to decline. They never caught up to the group that started on rivastigmine initially. Similar findings were seen with galantamine and donepezil (73,80). An open-label extension study found that the group that was started on donepezil (10 mg/day) and continued on this dosage functioned better for 18 to possibly 24 months longer than persons who were initially on placebo and then started on donepezil (10 mg) (80). These findings indicate the importance of starting ChEI as early as possible in AD. Early institution of ChEI may also delay the emergence of neuropsychiatric symptoms in patients with mild to moderate AD, as shown in a 5-month placebo-controlled study with galantamine (82).

More Advanced AD and ChEI Therapy

There is preliminary evidence that the beneficial effects of ChEIs may extend to more advanced (moderate to severe AD) stages and that effects may even be more robust than seen in mild to moderate AD (83). In this 24-week, randomized, double-blind placebo-controlled study, the donepezil group showed significant improvement in the neuropsychiatric inventory (NPI) scores, whereas the placebo group worsened slightly. The donepezil group was better than the placebo group for all individual items in the NPI, with statistically significant differences seen for depression, anxiety, and apathy (83).

Treatment of AD With ChEIs in the Nursing Home Setting

Very little controlled data is available for the potential benefits of ChEIs in patients with AD in the LTCF setting.
Donepezil was found to be beneficial in the domain of cognition and overall dementia severity compared to placebo in a 6-month treatment period of AD patients in the nursing home setting (84). Unfortunately, no significant differences were obtained in the noncognitive domains of behavioral disturbances and ADL in this study. An open-label, 52-week study of rivastigmine in nursing home patients with AD demonstrated improvement in many of the behavioral and psychiatric symptoms, such as irritability, anxiety, delusions, hallucinations, disinhibition, aberrant motor activity, nighttime behavior, and appetite (85). In addition, about 40% of patients who were on neuroleptic medications for these symptoms were able to reduce or discontinue these medications over the course of the study. Patients with AD in the nursing home are generally older, exhibit greater severity of dementia, and have more comorbid illness than do AD patients in the community.

Use of ChEIs in Non-Alzheimer’s Dementias

ChEIs are approved for use in mild to moderate AD only, and use of these agents to treat other dementing disorders is an off-label use. There is initial evidence from randomized, double-blind, placebo-controlled studies that ChEIs may also benefit cognition, daily functioning and behavioral symptoms in vascular dementia (VaD) and Lewy body disease/dementia (LBD) (86–88). Both of these dementing disorders have been found to have an associated cholinergic deficit. Preliminary data indicates that early and widespread cholinergic losses may help differentiate LBD from AD (89), suggesting that cholinergic replacement therapy may be even more effective in LBD than in AD, especially in mild-stage disease. We recommend a trial of ChEIs for patients with VaD and LBD. Other disorders associated with cholinergic deficit include but are not limited to Parkinson’s disease with dementia and Down’s syndrome with progressive cognitive decline. These disorders may also benefit from a trial with ChEI, although large controlled studies are lacking. The only double-blind, placebo-controlled 24-week pilot study in patients with Down’s syndrome and AD showed that improvement in the donepezil group was not significantly better than improvement with placebo. Surprisingly, noncognitive symptoms showed less improvement than they did in the placebo group (90). The biological basis of these findings is not yet certain. No therapeutic benefit is anticipated in dementia syndromes without a cholinergic deficit, such as frontotemporal dementia or Huntington’s dementia. Nonprogressive dementias, such as those secondary to traumatic brain injury or anoxic encephalopathy, may also not respond to ChEIs.

Patient Selection, Management of Adverse Effects, and Therapeutic Outcome

All pivotal studies have investigated patients with mild to moderate AD. How early in the course of AD ChEIs should be initiated and for how long they are of use have not been elucidated fully. Although most studies have been done in patients with mild to moderate AD (Mini-Mental State Exam [MMSE] scores between 10 and 26), clinicians are recommended to consider ChEI even in patients with AD and scores of more than 26 or less than 10. We recommend that patients should continue on these medications until they no longer have meaningful interactions with other individuals, because ChEIs may still help alleviate behavior problems even when cognition is severely impaired. Several factors influence medication prescribing for most older patients with AD, resulting in considerable variability and the need to individualize treatments. Elderly patients often take multiple medications, so the clinician must be aware of potential drug interactions. Patients with symptomatic bradycardia, active peptic ulcer disease, and acute exacerbation of chronic obstructive pulmonary disease and asthma may experience worsening of their problems because of the mild peripheral cholinergic effects of ChEIs. Generally, ChEIs can be safely instituted once these conditions are stabilized. Adverse effects are similar for all ChEIs and typically are gastrointestinal (nausea, vomiting, diarrhea, anorexia, and weight loss) in nature. They are usually seen during dose escalation. Other adverse effects such as abdominal pain, dizziness, syncope, and headache have been also described but are less common. Adverse effects are usually mild to moderate in severity and resolve spontaneously or after dosage reduction. The frequency of adverse effects dramatically increases when the dose of a ChEI is increased too rapidly (in 1–2 weeks). Their frequency is very low during the maintenance phase. Potential for prolonging the effects of the muscle relaxant succinylcholine, used during anesthesia, exists with all ChEIs but does not seem to be clinically significant, although the anesthetist should be informed of the possibility. We do not recommend discontinuing these drugs a few days prior to surgery because of the risk of cognitive deterioration. If for any reason a ChEI is discontinued for a significant period and need to be re-instituted, it should be done by again starting at the lowest dose and gradually titrating upward to the highest tolerated therapeutic dose. These drugs have not been well studied in patients with severe hepatic or renal impairment. Hence, caution should be exercised when using a ChEI in this patient population.

Dose titration should be as slow as necessary to prevent the development of gastrointestinal or other side effects. The risk of nausea can be reduced by administering the medication on a full stomach, and intermittent antiemetics can be used if necessary. Patients should be titrated up to the highest therapeutic dose they can tolerate (for donepezil it is 10 mg/day, for rivastigmine it is 12 mg/day, and for galantamine it is 24 mg/day). Once therapy with ChEI is begun and the therapeutic dosage reached, patients should be evaluated every 3 months to monitor response to treatment in 3 domains, cognitive, functional, and behavioral. If unacceptable side effects occur at higher doses, the dose should be decreased as long as it is in the therapeutic range. If side effects develop with dose escalation, we recommend going back to the tolerated dose and then increasing the interval of dosage escalation. ChEI should be discontinued if side effects persist at the lowest therapeutic dose, if the patient shows accelerated decline after a 6-month trial, or if a medical condition develops that significantly increases the risk benefit ratio. The lowest therapeutic dose is 5 mg/day for donepezil, 6 mg/day for rivastigmine, and 16 mg/day for galantamine. If patients with AD are not able to tolerate
more than donepezil 5 mg/day, rivastigmine 3 mg/day, or galantamine 8 mg/day, another agent should be considered. Patients who have been on one ChEI and failed to benefit (due to intolerable side effects or accelerated decline) should be considered for a trial with another ChEI. Incontinence and increased behavioral disturbances (irritability) have been described with donepezil use and may be seen with other ChEIs as well.

The course of AD tends to be slowly progressive, with a loss of 3–5 points per year on a standard assessment instrument such as the MMSE. Caregivers and patients must have realistic expectations (Table 4); these drugs’ effects are modest, and sometimes no symptomatic improvement is noted. In fact, a report of ‘no change’ means that these drugs are helping, because without ChEI treatment, one would have seen a decline in functioning.

If a ChEI is stopped, rapid deterioration can occur in some patients. Also, reintroducing the drug after the AD patient has been taken completely off a ChEI may not yield the same benefit. By tapering the dosage slowly, we can detect early those patients who are going to lose function or show cognitive deterioration. If they do, then there exists a good reason not to take them off the drug. Only very early in the disease will the patient be able to self-report improvement or benefit. Many of the patients, by the time they are diagnosed, have already lost insight and are unable to appreciate the benefits of ChEIs.

Other Agents for Treatment of AD

**Metrifonate.**—Metrifonate is another ChEI that has been investigated for the treatment of mild to moderate AD. Metrifonate was found to be beneficial in areas of cognition, global functioning, and ADLs, compared to placebo in patients with mild to moderate AD, in a meta-analysis of 4 randomized, double-blind, placebo-controlled trials (91). Unfortunately, development of this agent was halted recently secondary to problems with muscle weakness and respiratory paralysis.

**Memantine.**—Memantine, a noncompetitive, highly voltage-dependent NMDA antagonist, has been approved for use in the treatment of dementia in Germany for over 10 years and recently was approved for use in the treatment of AD in the European Union. It has been found to be useful in more advanced (moderate to severe) cases of AD (92). Patients with AD in the United States may import the drug or consider participating in double-blind, placebo-controlled studies currently underway at numerous sites all over the country. The FDA is currently reviewing the data for approval of its use in the United States.

**Ginkgo biloba extract.**—Oken and colleagues reviewed the published literature on efficacy of Ginkgo biloba for AD (93). They identified 4 well-designed, randomized, placebo-controlled studies that met their inclusion criteria. They concluded that treatment with Ginkgo biloba extract (120 to 240 mg/day for 3–6 months) had a small but significant effect on objective measures of cognitive function in AD. We need further research to determine whether there is improvement in noncognitive behavioral or ADL functions with Ginkgo biloba extract, since this is critical in evaluating the use of treatment in AD. Also, there is no data regarding the safety of the use of Ginkgo biloba extract along with ChEIs.

**Antioxidants** (vitamin E and selegiline).—In a double-blind, randomized, placebo-controlled study (94), fewer participants (58%) in group taking vitamin E (2000 IU/day) and selegiline (5 mg bid) reached 1 of the 4 endpoints (death, institutionalization, loss of 2 out of 3 basic ADL, or severe dementia), compared to 74% with a placebo. However, more participants taking vitamin E suffered a fall compared to patients receiving a placebo. It was not possible to interpret the reported results for specific endpoints (95). There was no difference between the vitamin E group and the selegiline group. There appeared to be no additive benefit to treatment with both agents. The principal concerns with high-dose (2000 IU) vitamin E are gastrointestinal upset and prolonged clotting time, with easy bruisability or bleeding. A lower dose (400 iu bid) of vitamin E is recommended by many experts for patients with AD and may be associated with lowered risk of adverse effects without compromising the beneficial effects. In patients with AD, selegiline leads to small short-term improvement in cognition and activities of daily living. Selegiline does not improve emotional state or global response (96). For patients with AD who can tolerate vitamin E, there is no reason to take selegiline.

**Estrogen.**—Clinical trials indicate that oral conjugated equine estrogen is not an effective treatment for AD in postmenopausal women (97,98). Hence, estrogen is not recommended for the treatment of cognitive or functional deficits attributable to AD. Preliminary data indicate that short-term estrogen therapy may safely decrease the frequency and severity of behavioral disturbances of dementia in elderly patients (99,100). Larger randomized, controlled studies are needed to further explore the potential benefits of estrogen in the treatment of behavioral disturbances (aggression, sexual disinhibition) in patients with AD. There is increasing evidence that estrogen may decrease the risk for or

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**Table 4. Clinical Expectations From Cholinesterase Inhibitor Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Primary benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maintain current level of daily functioning or slow the decline in current level of functioning</td>
</tr>
<tr>
<td></td>
<td>Maintain current level of cognition or slow the cognitive decline associated with Alzheimer’s disease (AD)</td>
</tr>
<tr>
<td></td>
<td>Decrease emergence of behavioral and psychological disturbances associated with AD</td>
</tr>
<tr>
<td>Secondary benefits</td>
<td>Decrease caregiver burden and distress</td>
</tr>
<tr>
<td></td>
<td>Decrease overall health-care cost</td>
</tr>
<tr>
<td></td>
<td>Delay institutionalization</td>
</tr>
<tr>
<td>Caregiver and physician expectations</td>
<td>“No change&quot; means cholinesterase therapy is helping</td>
</tr>
</tbody>
</table>

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delay the onset of AD in postmenopausal women (101,102). However, this has not been universal (103,104), and a number of methodological shortcomings in these studies have been identified (105). These potential benefits have to be weighed against the known risks of estrogen, such as increased risk of thromboembolism and gynecological cancers.

**TREATMENT OF BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF AD**

The most challenging aspect of AD care is management of behavioral and psychological signs and symptoms of dementia (BPSD) (106,107). BPSD are common, serious problems that affect the quality of life of both patient and caregiver and that frequently result in premature institutionalization. The majority of BPSD in AD are of clinical significance based on their severity and because of co-occurrence of multiple symptoms (108). BPSD are associated with more rapid rates of cognitive and functional decline. BPSD include agitation, aggression, delusions, hallucinations, depression, apathy, sleep disturbances, and sexually inappropriate behaviors (Table 5). These difficulties occur in 90% of patients at some point in the course of the disease and have been described in all dementing illnesses. Many clinical practice guidelines (109,110) have addressed the treatment of these disturbances, noting that even modest improvement in these behaviors can markedly improve quality of life for both patient and caregiver. Practice guidelines frequently recommend starting with behavioral and environmental approaches, followed by a wide variety of pharmacologic interventions, including antipsychotics, antidepressants, and anticonvulsants. For a comprehensive review of management of BPSD in patients with AD, the reader is referred to the review article on recognition and management of behavioral disturbances in dementia by the authors (107).

Figure 1 provides an algorithm for the management of behavioral disturbances in patients with Alzheimer’s disease (AD).
They need to know they are loved and they need to feel good. They are still people, with the same emotional needs as all people. Unstructured activities improve subjective well-being, while structured activities may in turn generate a sense of helplessness and hopelessness, depression, and a loss of control over their destiny, and patients are at risk of invalidism, social isolation, lower self-esteem, depression, and a loss of control over their destiny, which may in turn generate a sense of helplessness and hopelessness. Inactivity also increases the risk of pressure sores, falls, loss of range of motion, and muscle wasting. Structured and unstructured activities improve subjective well-being, help maintain function, and decrease BPSD. People with AD are still people, with the same emotional needs as all people. They need to know they are loved and they need to feel good.

NONPHARMACOLOGICAL INTERVENTIONS

Nonpharmacological interventions are the key to management of BPSD. The majority of AD patients are calmer and better adjusted when treated with low-tech, nondrug approaches that help to decrease problem behaviors and promote independence (Table 6). The foundation of nonpharmacologic management is recognizing that the person with dementia is no longer able to adapt and that instead the environment must be adapted to the patient’s specific needs. Caregivers should be counseled to learn to change what can be changed through information gathering and direct action. They must also train themselves to cope with their reactions to what cannot be changed (and “intrapsychic” tricks or reframing perspectives—“tomorrow will be better,” “my husband is difficult but he could be worse”). Positive outcomes derived from support groups include not only increased knowledge of the illness and services available as well as decreased feelings of isolation but also creative and practical suggestions for dealing with BPSD using nonpharmacological interventions. Adult day services are often an effective method for managing demented patients and postponing the need for institutionalization. Caring for loved ones with AD is psychologically and physically challenging but also provides the family with opportunities for personal growth and deepening of relationships with the patient and other family members. Behavioral disturbances are often provoked through interaction with caregivers. The manner in which caregivers approach the patient with AD is critical, because most episodes of aggressive behavior occur during contact with caregivers. Effective strategies include leaving the patient and returning later or having one caregiver distract the patient while another is providing care. As ADL dependence on others increases, patients are at risk of invalidism, social isolation, lower self-esteem, depression, and a loss of control over their destiny, which may in turn generate a sense of helplessness and hopelessness. Inactivity also increases the risk of pressure sores, falls, loss of range of motion, and muscle wasting. Structured and unstructured activities improve subjective well-being, help maintain function, and decrease BPSD. People with AD are still people, with the same emotional needs as all people. They need to know they are loved and they need to feel good about themselves, to be respected, to have the approval of others who are important to them, to be stimulated in body, mind, and spirit, to feel secure, to be included (not alienated and marginalized), and to be needed. Every effort must be made by the health-care providers to assist the caregivers in meeting these needs of patients with AD. Some more-specific nonpharmacological interventions are as follows:

1. People with very early or mild AD who have been told their diagnosis and prognosis are faced with psychological problems that may be helped by regular counseling or psychological support.

Table 6. Nonpharmacological Interventions for the Treatment of Alzheimer’s Disease (AD)

<table>
<thead>
<tr>
<th>Interventions with the patient</th>
<th>Specific nonpharmacological interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior-oriented approaches</td>
<td>Behavioral treatment (increasing pleasant events): especially useful for treatment of depression in moderate stages of AD</td>
</tr>
<tr>
<td></td>
<td>Describe the problem behavior, assess specific antecedents and consequences and implement specific strategies suggested by the first 2 steps</td>
</tr>
<tr>
<td>Emotion-oriented approaches</td>
<td>Supportive psychotherapy: especially in early stages of AD</td>
</tr>
<tr>
<td></td>
<td>Reminiscence therapy: in mild to moderate stages of AD</td>
</tr>
<tr>
<td></td>
<td>Validation therapy: in mild to moderate stages of AD</td>
</tr>
<tr>
<td></td>
<td>Simulated presence therapy: in moderate to severe stages, especially for patients in long-term care facilities</td>
</tr>
<tr>
<td>Cognition-oriented approaches</td>
<td>Cognitive therapy: especially for treating depression in early stages of AD</td>
</tr>
<tr>
<td>Stimulation-oriented approaches</td>
<td>Recreational therapies (crafts, games, pets)</td>
</tr>
<tr>
<td></td>
<td>Art therapies (music, dance, art)</td>
</tr>
<tr>
<td>Non-specific nonpharmacological interventions</td>
<td>Reassurance</td>
</tr>
<tr>
<td></td>
<td>Distraction</td>
</tr>
<tr>
<td></td>
<td>Bright-light therapy</td>
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<tr>
<td></td>
<td>Touch therapy: hand massages, back rubs</td>
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<tr>
<td></td>
<td>One-to-one therapy</td>
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<tr>
<td></td>
<td>Gardening</td>
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<tr>
<td></td>
<td>Aromatherapy</td>
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<td></td>
<td>Light exercise</td>
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</table>

Interventions with the family member/caregivers

<table>
<thead>
<tr>
<th>Interventions to benefit the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem-solving therapy for the caregivers: especially for treating depression in moderate stages of AD</td>
</tr>
<tr>
<td>Skills training for the caregivers: to improve personal care skills</td>
</tr>
<tr>
<td>Structured educational programs to decrease use of inappropriate medications and psychotherapeutic agents for behavioral and psychological symptoms of AD (BPSD)</td>
</tr>
<tr>
<td>Interventions to benefit the family member/caregivers</td>
</tr>
<tr>
<td>Family therapy: especially to address conflicts, abuse</td>
</tr>
<tr>
<td>Support groups: to decrease loneliness, increase knowledge of illness and services available, and learn creative and practical nonpharmacological interventions</td>
</tr>
<tr>
<td>Psychoeducational groups</td>
</tr>
<tr>
<td>Self-help groups</td>
</tr>
<tr>
<td>Respite care</td>
</tr>
<tr>
<td>Cognitive behavioral approaches: especially for treatment of depression in the caregiver</td>
</tr>
</tbody>
</table>

Caring for loved ones with AD who have been told their diagnosis and prognosis are faced with psychological problems that may be helped by regular counseling or psychological support.
2. In the early stages of AD, patients can use diary and dictaphone to help them remember events and conversations. Patients should try and concentrate on doing things they are good at, rather than pursuing tasks they cannot manage.

3. The desire to “go home” is common in people who have AD, even when they’re still residing in the homes in which they have lived independently for years. The caregiver should avoid correcting the patients or reassuring them that they are in their homes. It is better to inquire where home is and who the patients might be worried about there.

4. Often people with dementia report being worried about their young children—even though they’re now grown—or about their parents—even if they’re deceased. We recommend reassuring these persons that everyone at home is OK and that those at home know that the patients are OK. Asking what the patients like best about “home” and helping patients with AD to reminisce about the good times in the home are also beneficial.

5. People with AD may curse or use language that the family finds shocking. This may be a sign that the person has lost inhibition and impulse control and now says the first thing that enters his or her mind. It’s important to remind the caregivers that this isn’t intentional and should not be taken personally.

6. The caregivers should listen attentively and watch for nonverbal clues that might indicate hunger or thirst, implied meanings, and expressed feelings.

7. Caregivers need to adjust their expectations regarding a loved one with AD throughout the course of the illness. Activities such as folding and stacking items gives the person with AD a sense of purpose and accomplishment. Maintaining a routine of meaningful activities that promote success is important for people with AD, whose days are filled with frustration and failure.

8. Religious worship is a safe and soothing activity for many persons with AD. It enables them to respond to their faith and spiritual needs through long-remembered rituals that connect past and present. For persons living alone, members of the congregation may be the first to notice the early signs of AD.

9. Although a recent randomized, controlled trial did not find walking and or talking to provide any benefits in communication, ambulation, and functional status in residents with AD (112), exercise has been documented to improve muscle strength (thereby reducing frailty, functional decline, and injuries), even in frail residents in nursing homes (113,114). In addition, walking and other forms of light exercise may decrease problem behaviors.

10. Meaningful activities may improve depression and diminish agitation, apathy, insomnia, and repetitive vocalization.

11. Graded assistance, practice, and positive reinforcement should be used to increase functional independence.

12. Patients with AD may experience decreased problem behaviors with music, particularly during meals and bathing.

13. Use of therapeutic touch, including massage, may decrease agitation/irritability (115).

Specific Therapies/Approaches and Their Efficacy

Whatever the intervention, it is critical to match the level of demand on the patient with his or her current capacities, avoiding both infantilization and frustration, and to modify the environment insofar as possible to compensate for deficits and to capitalize on the patient’s strengths.

Behavior-oriented approaches.—Behavioral approaches can be effective in lessening or abolishing problem behaviors. The steps involve careful description of the problem behavior, assessment of specific antecedents and consequences, and implementing specific strategies that are often suggested from the first 2 steps (116).

Emotion-oriented approaches.—These interventions include but are not limited to supportive psychotherapy, reminiscence therapy, validation therapy, sensory integration, and simulated presence therapy (116–120). These interventions have been shown to improve mood and behavior.

Cognition-oriented approaches.—These techniques include reality orientation and skills training (121,122). These interventions have shown slight transient improvement in cognition, but there have also been reports of anger and frustration. The slight improvements observed with some of these treatments have not lasted beyond the treatment sessions and thus do not appear to warrant the risk of adverse effects.

Stimulation-oriented approaches.—These treatments include activities (structured and unstructured) or recreational therapies (e.g., crafts, games, pets) and art therapies (e.g., music, dance, art). There is some evidence that, while they are in use, these interventions decrease behavioral problems and improve mood (123–125).

Interventions for Families and Caregivers

Practical and creative problem solving, prayer, humor, the dependable support of family and friends, expressive outlets, the ability to forgive others and one’s self, and learning how to economize the personal and family “energy” that is available, for example, can all be effective coping strategies that families and caregivers should be encouraged to use. For families who are struggling with various aspects of the issues that arise while caring for a patient with AD, sessions of family therapy have proven beneficial (126). For alleviating caregiver and family distress, a broad array of psychosocial interventions was assessed in a meta-analysis of 18 studies (127). The interventions included psychoeducation, support, cognitive-behavioral techniques, self-help, and respite care. Exercise has been shown to improve caregiver outcomes (128). Individual and respite programs were found moderately effective at reducing caregiver burden and dysphoria, but group interventions were only marginally effective.

Subsequent research buttressed the utility of adult day care in reducing caregiver’s stress and depression and in enhancing their well-being (129). Targeted behavioral techniques also improved the quality of caregivers’ sleep (130), whereas psychoeducation and family support appeared to
promote better patient management. A range of behavioral interventions for nursing home staff have been shown to be effective in improving behavioral symptoms of AD, such as incontinence (131,132), dressing problems (133), and verbal agitation (134,135). A major problem is that interventions are not maintained or implemented correctly by nursing home staff (136). Additional patient and caregiver benefits may be obtained by the use of computer networks to provide education and support to the caregivers.

Depression

Population studies have shown that major depression occurs in 12% of demented patients, while higher percentages have been reported in clinical samples. Depressive symptoms are much more common in AD than major depression and affect more than 30% of these patients (137). Depressed mood and anhedonia have been identified in 49% of AD patients; these symptoms do not correlate with either vegetative symptoms or cognitive symptoms of depression. Family history of depressive disorders increases the probability of developing depression during the course of AD. Common depressive symptoms and signs in AD in those who do not meet criteria for major depression include loss of interest, lack of energy, thinking and concentration difficulties, and psychomotor disturbances. Depressive symptoms as a rule do not coexist with apathy in demented patients (138). Apathy appears to be a syndrome distinct from depression, and its prevalence increases as the cognitive impairment in AD increases (138). Depressive symptoms add to functional impairment of AD patients and are associated with increased psychopathology in their caregivers. If left untreated, depressive symptoms or syndromes persist or subside to some extent and then recur. As AD progresses, depressive symptoms become less prominent and often are overshadowed by other behavioral abnormalities, including delusions, aggressive behavior, and agitation. Depression of AD involves fewer required symptoms than a major depressive episode, and less emphasis is placed on verbally weighted items. Provisional diagnostic criteria for depression of AD have been proposed (139). Health-care providers need to be aware that suicide attempts are not rare in AD patients (140). Thus, all AD patients with depression should be carefully evaluated for suicide potential. Treatment is likely to be of value, with reported response rates of up to 85% (141).

There is some evidence that it is possible to modify cognitive-behavioral therapies for depression to allow them to be administered to patients with mild dementia and to modify behavioral therapies to allow them to be provided for those with moderate to severe dementia (142,143). Cognitive therapy, seen as more promising in the early stages of dementia, strives to help patients cope with depression by reducing cognitive distortions and by fostering more adaptive perceptions (142). Behavioral therapy, seen as more promising for more moderately or severely affected adults with dementia, targets family caregivers directly—and patients indirectly—by helping caregivers identify, plan, and increase pleasant activities for the patient, such as taking a walk, designed to improve their mood (130). Further affirmations for behavioral therapy for depression of patients with AD was provided by a controlled clinical trial (144). In this randomized clinical trial, researchers compared 2 behavioral therapies with a typical care condition, in which family caregivers were given information, advice, and support in their efforts to manage patient problems, and a wait list control in 72 individuals who had major depression and AD (145). One type of behavioral treatment consisted of teaching caregivers to focus on increasing pleasant events for the patient, while the other focused on improving the caregivers’ approach to problem solving. Those in the 2 behavior therapy conditions and those in typical care received the intervention in the form of 9 weekly, 60-minute sessions. The study provided strong support for the efficacy of specific psychosocial treatments; the 2 behavior therapy conditions were equally beneficial in reducing depressive symptoms and were superior to both the typical care and wait list conditions. Outcomes were similar for the typical care and wait list conditions, suggesting that, in the absence of a structured approach to treatment, professional contact alone is not effective. Depressed mood may also respond to improvements in living situation or stimulation-oriented treatments.

Somatic treatments for depression can be used in demented patients to improve mood, functional status, and quality of life. These treatments should be considered even for patients with depressed mood who do not meet the diagnostic criteria for major depression (132). Patients with severe or persistent depression should be treated with antidepressants. The choice among agents is based on the side effect profile and the characteristics of a given patient. Selective serotonin reuptake inhibitors (e.g., citalopram, sertraline, paroxetine) are probably the first-line treatments and are supported by many RCTs, although other agents such as mirtazapine and venlafaxine may be more appropriate for some patients (146–150). Electroconvulsive therapy (ECT) is effective in the treatment of depression in dementia patients (151). ECT may be beneficial for patients with severe major depression who are ineligible for, cannot tolerate, or do not respond to antidepressants (152). Individuals whose cognitive symptoms recover fully with treatment of depression are considered not to have been demented but rather to have a condition called dementia syndrome of depression; however, about half of such persons may develop dementia in 5 years (153). The management of depression has been reviewed in detail in a recent issue of the Journal (154).

Psychotic Symptoms

It is estimated that approximately 30–50% of patients with AD develop delusions and hallucinations at some point during the course of AD (155). Psychosis with AD may run in families (156). The psychotic symptoms consist of nonelaborate persecutory delusions (e.g., accusations of someone stealing the patient’s possessions) and simple visual or, less commonly, auditory hallucinations. Psychotic symptoms often cause severe agitation and aggression as well as emotional distress and may precipitate institutionalization or hospitalization.

Mild psychotic symptoms associated with AD are best managed with nonpharmacological interventions and cholinesterase inhibitors. If antipsychotics are used, the goals should be modest (reduction of emotional distress and
behavioral disturbances) and should not be resolution of psychotic symptoms. A dose decrease or discontinuation is recommended periodically for all patients with psychoses associated with AD who receive antipsychotic medications (157). The major predictors of relapse, if antipsychotics are discontinued, are agitation and aggressive features. Although conventional or typical antipsychotics (e.g., Haloperidol, thioridazine, chlorpromazine, perphenazine, fluphenazine, etc.) are somewhat better than placebo for psychosis of AD (158,159), the effect is modest, and the high risk of toxicity (especially extrapyramidal syndrome [EPS] and tardive dyskinesia [TD]) usually makes them inappropriate. Despite this, conventional antipsychotics continue to be chosen over atypical antipsychotics for psychotic symptoms and aggression in patients with dementia, even in industrialized countries (160). Even low-potency conventional antipsychotics (e.g., Thioridazine, chlorpromazine) are associated with high frequency of EPS in patients with AD. Risperidone has the largest body of currently available published evidence amongst the atypical antipsychotics for the treatment of psychoses associated with AD. Two 12-week, randomized, double-blind, placebo-controlled trials of risperidone included nearly 1000 test subjects who were suffering from dementia with psychosis and agitation (AD, VaD, and related disorders) (161,162). They found that 1 mg was the optimal dose. Doses of 0.5–1.5 mg daily do not produce a significantly increased incidence of side effects, but nonetheless they are effective in controlling psychosis-driven behavioral disturbances and aggression. Risperidone was superior to haloperidol in terms of efficacy, while presenting a significantly more benign side-effect profile. Risperidone at higher than 1.5-mg doses is associated with increased EPS, although in some patients with AD, EPS can occur even at lower dosages. Risperidone was found to be effective and well tolerated over 13–46 months for nursing home residents with dementia and behavioral disturbances, despite high rates of medical comorbidity and use of concomitant medications (163). A 6-week randomized, double-blind, placebo-controlled study of olanzapine was conducted in 206 nursing home patients with AD or VaD plus psychosis or severe agitation (164). Patients received either placebo or olanzapine in 5-mg, 10-mg, or 15-mg doses. The most effective doses turned out to be 5 mg or 10 mg. A 15-mg dose was not better than placebo but produced significant gait disturbance and sedation. In some patients with AD, gait disturbance can occur even at lower dosages. In a 10-week, double-blind, placebo-controlled, randomized trial with nursing home residents with dementia and psychosis, quetiapine (average dose 120 mg/day) was better than placebo in reducing symptoms of agitation but not psychosis (165). A large, multicenter, open-label study of quetiapine (average daily dose 100 mg) found it to be useful for psychotic symptoms in the elderly, many of whom had dementia (166). The most common side effects associated with quetiapine were somnolence and falls. Ziprasidone is the newest atypical antipsychotic, and to date there are very few data available in the elderly. Randomized, controlled studies are needed before ziprasidone can be recommended as the drug of first choice for treatment of psychosis of AD. Patients with AD and psychosis on conventional antipsychotics can be safely switched to atypical antipsychotics to minimize the risk of EPS and TD (167). Compared to conventional antipsychotics, atypical antipsychotic drugs cause less TD (168). Cholinesterase inhibitors may benefit mild psychotic symptoms in dementia patients (62,87). A recent study found the antidepressant citalopram to be more efficacious than placebo in the short-term hospital treatment of psychotic symptoms and behavioral disturbances in nondepressed, demented patients (169). These drugs may be considered in AD patients with psychotic symptoms before antipsychotics are considered.

Agitation

The most common behavioral disturbance associated with AD is agitation, which affects nearly three fourths of patients and typically increases in severity as the disease progresses. Agitation involves verbal and physical aggression, increased psychomotor activity, repeated verbalization, screaming, etc. Agitation often co-occurs with anxiety, psychotic symptoms, and irritability. However, clinicians should be sure to exclude potential causes unrelated to AD, such as pain, medical illness, medication adverse effects, or environmental provocation.

Mild to moderate agitation is best managed by nonpharmacologic interventions, as environmental factors and caregiver patient interaction can significantly influence agitation. Severe agitation may need a trial of psychotropics. Controlled clinical trials for the treatment of agitation have reported efficacy of atypical antipsychotics (161,162,164), antidepressants (148), beta-adrenergic blockers (170), and anticonvulsants (divalproex, carbamazepine) (171,172). A 16-week RCT in community-dwelling patients with AD and agitation did not find any statistically significant difference between the group receiving trazodone, the group receiving haloperidol, and the group receiving behavioral approaches (behavior management techniques to caregivers). There was slight worsening of cognition and function in the medication group (173). Uncontrolled studies and small controlled studies have suggested use of gabapentin and buspirone for the treatment of agitation (174,175).

Despite the widespread utilization of benzodiazepines (BZ) in community-dwelling elders as well as in the nursing home population, data supporting the use of BZ and other antianxiety agents in AD are very limited. BZ may be used for a short duration in AD patients who have moderate to severe free-floating anxiety or who may be apprehensive about particular events, such as medical procedures or admission to the hospital or a LTCF. Although treatment with BZ may be efficient in the short term, their long-term usage is limited by their gradual decline in efficiency and the potential side effects of sedation, decreased cognitive functioning, loss of coordination and unsteadiness, and paradoxical disinhibition of behavior (176). When indicated, a BZ with a short half-life, such as lorazepam or oxazepam, is recommended. BZ have not been rigorously investigated in AD, and their effectiveness in controlling behavioral disorders in patients with AD has not been conclusively demonstrated. BZ perform better than placebo but not as well as antipsychotics in reducing agitation in patients with AD (177). Discontinuation of BZ has been
found to improve cognitive performance in nursing home patients with dementia (178).

Sleep Disturbances

Sleep disorder is common in AD and may be manageable with nonpharmacologic interventions in many cases (179). The most disturbing sleep disturbances include day/night reversal of sleep pattern and the waking by the patient of the caregiver. Appropriate sleep hygiene (including regular sleep and waking times, limited daytime sleeping, avoidance of fluid intake in the evening), calming bedtime rituals, and adequate daytime physical and mental activities should be tried before pharmacological interventions. There is preliminary evidence from 2 small open trials for elderly subjects with dementia (180,181) suggesting that early-morning or evening bright-light therapy may improve sleep (and possibly behavior as well). It is important to investigate sleep disorders such as restless leg syndrome, REM sleep behavior disorder, nocturnal myoclonus, and sleep apnea, which are relatively common in elderly individuals. Sleep apnea contraindicates the use of benzodiazepines or other agents that suppress respiratory drive. Short-term use of zolpidem (5–10 mg) may be considered in certain situations (182). Other drugs that may be tried judiciously include trazodone and sedating antidepressants such as mirtazapine. Benzodiazepine (lorazepam, temazepam) use should be limited to short-term use for a few days in certain situations, such as a short hospital stay. Any drug used as a sleep aid can increase the risk of falls. Patients should be counseled not to use over-the-counter sleep aids containing anticholinergic agents such as diphenhydramine (present in Tylenol PM) because of risk of delirium and hallucinations.

Initiating, Monitoring, and Maintaining Safe Pharmacologic Treatment for BPSD

Selection of the right drug and the proper dosage should be guided by the nature of the patient’s symptoms (Tables 7 and 8). A drug should be continued as long as it is effective, but no longer than needed. Its efficacy can be gauged more easily if realistic goals have been set and target behaviors specified before initiating treatment. Achieving significant efficacy may require a few weeks of treatment. Rapidly switching from one agent to another deprives the patient of an adequate trial. Recent data on beneficial effects of ChEIs and antidepressants on behavioral disturbances including psychotic symptoms and agitation suggests that the intuitive approach of treating agitated AD patients experiencing psychotic symptoms with antipsychotics may not be the safest approach for many patients.

Preventing Premature Institutionalization

ChEI may postpone nursing home placement for AD (183,184). Day care for people with AD can delay institutionalization. Potentially treatable BPSD are risk factors for institutionalization, and treating these symptoms might delay or prevent institutionalization. A comprehensive support and counseling intervention for spouse-caregivers of patients with AD reduced time to nursing home placement by nearly 1 year, compared with those not receiving the intervention (24,25). Interestingly, one of the key components of that intervention was to teach the caregivers behavioral management techniques to reduce difficult patient behaviors. Many of these interventions can be easily combined and may have an even greater impact on delaying institutionalization.

Factors Modifying Treatment Decisions

Treatment of Comorbidities

Several diseases are more common in AD because they are a consequence of the dementing process. These diseases include new onset seizures, respiratory and urinary infections, Parkinsonism, and pressure sores (185). In one study, more than 60% of patients with AD suffered from 3 or more comorbid conditions and complaints; virtually all (93%) had at least 1 (186). A case-control study using 7195 death certificates found that patients who died of AD had higher incidences of Parkinson’s disease, seizures, sensory impairments, infections, malnutrition, hip fractures and other injuries, and pressure sores, compared to control subjects (187). Treatment of individuals with advanced AD should weigh the possible benefits for the patient against the burden imposed by such treatment. Most medical interventions cause discomfort, especially to patients with dementia (56). Patients with advanced AD do not recognize the need for therapeutic interventions, do not cooperate with treatment, and often actively oppose it. Minor routine procedures, such as blood drawing or blood pressure measurement, typically precipitate behavioral disturbances. The dementing process also may limit the benefits of therapeutic interventions because of reduced life expectancy and decreased treatment effectiveness. Preventive measures, such as restricted diets and screening procedures, are appropriate only in the earlier stages of AD. Similarly, treatment of chronic conditions such as hypertension and diabetes should be aggressive only in the earliest stages of AD. In more advanced stages, treatment of comorbidities should be conservative and directed toward prevention of potentially serious side effects (e.g., postural hypotension that may lead to falls and hip fracture).

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily Dose</th>
<th>Indicated Clinical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Starting (mg) 10, Therapeutic (mg) 20–40</td>
<td>Depression, anxiety, agitation</td>
</tr>
<tr>
<td>Sertraline</td>
<td>25 mg, 50–100 mg</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10 mg, 10–20 mg</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>7.5–15 mg, 15–30 mg</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5 mg, 75–150 mg</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.25 mg, 0.5–1.5 mg</td>
<td>Psychosis, aggression</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5 mg, 5–10 mg</td>
<td>Psychosis, aggression</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25 mg, 50–200 mg</td>
<td>Psychosis, aggression</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>125 mg, 500–1000 mg</td>
<td>Mania, aggression</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>100 mg, 200–600 mg</td>
<td>Mania, aggression</td>
</tr>
</tbody>
</table>

SSRI = selective serotonin reuptake inhibitor.
Antibiotic therapy preferably should be limited to oral preparations. Intravenous therapy is to be avoided in moderate to severe AD patients because the demented patients in advanced stages do not understand the need for the medication and frequently try to remove the intravenous catheters and often end up with physical restraints or psychotropic drugs. Intramuscular administration of antibiotics such as cephalosporins should be considered before intravenous therapy. The effectiveness of antibiotic therapy may be limited by the recurrent nature of infections in advanced dementia. Also, adverse effects of antibiotic use, such as gastrointestinal upset, diarrhea, allergic reactions, etc., should be factored in before the decision is made to administer the drug.

**Urinary Incontinence**

Behavior modification, scheduled toileting, and prompted voiding should be used to reduce urinary incontinence. Urinary incontinence with donepezil has been reported (188), and all ChEIs have a potential to precipitate or exacerbate this problem. Treating urinary tract infection, fecal impaction, and other causes of urinary incontinence may suffice in many cases. Use of anticholinergic agents such as tolterodine and oxybutynin should be minimized, as these drugs may counteract the effects of ChEIs.

**Delirium**

Delirium is a significant problem for patients with AD, and it occurs much more frequently than it does in cognitively intact patients (189). Possible causes of delirium include an acute illness (urinary tract infection, respiratory infection) or medication toxicity. Compounds with anticholinergic effects (e.g., tricyclic antidepressants, low-potency antipsychotics, diphenhydramine, disopyramide phosphate) or histamine-2 activity (cimetidine, ranitidine) are particularly likely to cause delirium, but many other classes of medications can do so (190). Many of these medications are considered potentially inappropriate for use in the elderly (191). Avoidance of unnecessary medications, use of the lowest effective dose, using medications with least anticholinergic activity, vigilant monitoring aimed at early recognition, a thorough search for causes, and prompt treatment may diminish the prevalence and morbidity of delirium.

**Neurologic Issues**

In later stages, extrapyramidal signs such as rigidity may become prominent, especially in patients treated with antipsychotic drugs (even the more modern “atypical” agents). Seizures have been reported in 10–20% of AD patients, again, often late in the disease (192). Anticonvulsants such as divalproex, carbamazepine, and oxcarbazepine may not only benefit seizures but may also decrease agitation and aggression in patients with late-stage AD. Myoclonus, or brisk irregular muscle contraction, occurs in 5–10% of AD patients (193). A high index of suspicion and treatment of seizures and myoclonus in later stages of AD is recommended. Recent epidemiological and clinicopathologic data suggest overlaps between AD and cerebrovascular lesions that may magnify the effects of mild AD pathology and promote progression of cognitive and functional decline (194). Many AD patients also have comorbid cerebrovascular disease (CVD) or risk factors for CVD. Good control of blood pressure, treatment of atrial fibrillation, and antiplatelet therapy, such as low-dose aspirin, may help prevent further strokes.

**SITE-SPECIFIC ISSUES**

**Emergency Room (ER), Inpatient General Medical, or Surgical Services**

Patients with AD visit the ER twice as often as unaffected patients with similar conditions; these patients also remain hospitalized for a longer time (195). Lyketsos and colleagues reported that hospitalized patients with dementia had longer stays, higher costs, and a greater frequency of medication-induced psychosis and delirium (196). Statistically significant findings were discerned despite the likelihood that many cases of dementia were unrecognized, which reflects the substantial impact of dementia on clinical services. For many patients with AD, hospitalization represents a failure to prevent an unintentional injury, properly manage a chronic disorder, or use an appropriate alternate therapy, such as Hospice or temporary LTCF stay. Transfer of AD individuals to an ER or hospital exposes patients with AD to serious risks, such as increased confusion, agitation, anorexia, incontinence, and falls (197). These risks and potential benefits of treating acute medical problems should be discussed with the family before transfer. The risks are even higher in more advanced AD patients because of the very low rates of successful outcome in terms of improved survival and quality of life after treatment. Transfer to an ER or hospital should be used only when it is consistent with the overall goals of care and not as a default option. Having family members or aides stay with the patient may help decrease agitation and wandering that may occur in hospitalized patients with AD.

**Table 8. Principles of Pharmacotherapeutic Management of Behavioral Disturbances in Dementia Patients**

<table>
<thead>
<tr>
<th>Principle</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Use drugs only when secondary causes (environmental, medical) of behavioral disturbances have been ruled out and nonpharmacologic interventions have failed.</td>
<td>Review current medications and consider tapering or discontinuing unnecessary, ineffective, or harmful medications.</td>
</tr>
<tr>
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<td>Consider adverse drug reactions or drug-drug interactions as a potential cause of behavioral disturbances.</td>
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<td>If pharmacotherapy is used, start low and go slow and use it in conjunction with nonpharmacologic interventions.</td>
</tr>
<tr>
<td>5. If pharmacotherapy is used, start low and go slow and use it in conjunction with nonpharmacologic interventions.</td>
<td>Select agents based on target symptoms, side-effect profile, and individual patient characteristics.</td>
</tr>
<tr>
<td>6. Select agents based on target symptoms, side-effect profile, and individual patient characteristics.</td>
<td>Give the medication for an adequate time at an adequate dose.</td>
</tr>
<tr>
<td>7. Give the medication for an adequate time at an adequate dose.</td>
<td>Closely monitor for and document side effects and beneficial effects.</td>
</tr>
<tr>
<td>8. Closely monitor for and document side effects and beneficial effects.</td>
<td>If found beneficial, continue the medication for a few months. If the patient has been stable for that period, consider decreasing or discontinuing the medication.</td>
</tr>
<tr>
<td>9. If found beneficial, continue the medication for a few months. If the patient has been stable for that period, consider decreasing or discontinuing the medication.</td>
<td>Educate patient and family regarding the benefits and side effects of medications.</td>
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</table>
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Inpatient Psychiatric Units

Individuals with AD may need hospitalization to inpatient psychiatric units for the treatment of psychotic, affective, and behavioral symptoms that are causing harm to self or others, severe symptoms not responding to outpatient treatment, or if there is need for ECT (198,199). A thorough search for psychosocial, general medical, or noncognitive psychiatric difficulties that may be leading to the disturbance will often reveal a treatable problem. Both nonpharmacologic and pharmacologic interventions can be tried more readily and aggressively on inpatient units than in outpatient settings. Clinical experience suggests that patients with AD may not do well if treated in general adult units, where younger violent patients may pose some danger. Geriatric-psychiatry units, which are designed to address the unique needs of the demented patient with staff trained in the management of dementia patients, may be preferable.

Long-Term Care

According to the American Health Care Association, more than 1.5 million individuals in the United States reside in nursing homes. Within this population (elderly as well as nonelderly persons), 67–77% have dementia (100,201,202). Institutionalization offers many AD patients the best duration of survival, followed by a formal care package at home. In the nursing home, AD is underrecognized and undertreated. By the time patients with AD reach the nursing home, the bulk of their needs are no longer for health care but rather for custodial care. Most do not need high-tech care. They need care that is mediated by touch and delivered by professionals whose skilled eyes and hands can detect deterioration—professions who can intervene early and who can identify opportunities for improvement and rehabilitation. Psychoactive agents are one of the most prevalent class of drugs with potential for inappropriate use in elderly LTCF residents (203). Staff of LTCF should receive education about AD to reduce the use of unnecessary psychotropics. These facilities should be tailored to meet the needs of patients with dementia and to adequately address behavioral symptoms. Skills training for people with AD in LTCF may lead to an improvement in personal care skills. Structured activity programs can improve both behavior and mood (204). LTCFs need to take advantage of the latest thinking in design, which can help both staff and patients with AD. AD-specific design features include high levels of visual access, highly visible and signed toilet doors, indoor/outdoor wander-safe areas, increased lighting, age-appropriate fixtures and fittings, and individualized personal space (205). The interdisciplinary care model is recommended for patient care to best address the increasingly complex needs of AD residents in LTCF settings. The Omnibus Budget Reconciliation Act of 1987 regulates the use of physical restraints and many psychotropic medications in nursing homes. Health professionals practicing in nursing homes must be familiar with these regulations. Indications for antipsychotic medication treatment and available alternatives and outcomes should be carefully documented. A clinical strategy of carefully considering which patients may be appropriate for withdrawal of antipsychotic medications and for being prepared to maintain use of the medications in some cases and reinstate them in others, as deemed clinically necessary, is recommended. A structured education program for nursing and medical staff has been shown to decrease antipsychotic usage in the nursing home setting without adverse outcomes (206). Pet therapy and/or the introduction of the Eden Alternative may improve outcomes in some, but not all, patients with dementia (207–209).

Special Care Dementia Unit

The social environment is also significant in mollifying the behavioral manifestations of dementia. If demented individuals are grouped together on a special care dementia unit, many symptoms may be minimized. Grouping demented patients together further eliminates the problem of demented patients disrupting the routine of cognitively intact individuals by wandering into their rooms, rummaging through their belongings, or approaching them repeatedly with questions and unwanted physical contact. Well-designed studies are needed to demonstrate the benefits of such units.

Mild Cognitive Impairment (MCI)

MCI is a cognitive disorder with a high rate of conversion to AD over many years (210). Short-term memory loss is the most common abnormality. Patients with MCI perform similarly on memory tests when compared to patients with AD, but they perform similarly to normal elderly controls on other cognitive tests and in activities of daily living (197). Neuropsychiatric symptoms in MCI have a prevalence intermediate to that in healthy participants and those with AD (108). Recent evidence suggests that most patients with MCI eventually develop AD (211). Patients with MCI should be carefully evaluated and followed. Biological markers, including APOE, may be helpful in identifying patients at risk for conversion to dementia. While controlled trials for MCI treatments are in progress, patients may be offered empiric treatment with vitamin E and ChEIs. The potential for ChEIs to delay onset of dementia in patients with MCI is currently being rigorously investigated. Patients with MCI may be encouraged to participate in such studies with ChEIs.

The Future of AD Treatment

Pharmacotherapy

Definitely effective treatments for AD are few. Research to increase understanding of the underlying disease process and to seek new and better treatments is robust. Clinical research, with active patient participation, is a current and valuable means of treatment development for AD, with government- and private industry–sponsored therapeutic trials currently numbering in the hundreds. Epidemiological and postmortem studies have established a number of testable hypotheses (212). Secretase inhibitors (beta and gamma) may stall A-beta amyloid production, thus preventing neuronal plaque formation that is theorized to cause neuronal cell death. Such drugs are in a Phase-I stage of study. Beta-sheet blockers latch onto critical portions of spiral-shaped A-beta, helping them maintain their shape, thereby stalling the formation of new fibrils and allowing the body to clear A-beta from the brain, thus forestalling plaque formation. Such drugs are also currently in devel-
Development. Studies involving metal chelators such as desferrioxamine and clioquinol to reduce plaque formation are also underway. The theory behind this is that metals such as aluminum, iron, zinc, and copper promote A-beta aggregation and plaque formation, and drugs that bind to these metals (chelators) may prevent A-beta aggregation. Antibodies targeted to plaques (amyloid) can mark them for destruction by the immune system, resulting in increased clearance of plaque and reduced neuronal loss, and in animal studies, antibodies to beta-amyloid have enhanced memory (213, 214). An Alzheimer vaccine works on this principle and is currently under investigation. However, the initial human study with amyloid vaccine caused brain inflammation and had to be halted. New research with a more refined vaccine that has a higher degree of selectivity for the pathogenic target structures offers new hope (215). Blocking of A-beta production with an antisense directed against the amyloid precursor protein also improves memory in animals (216). Chronically high levels of glutamate have been implicated in causing neuronal cell loss. Glutamate antagonists such as memantine (which is already approved in Europe) may thus protect neuronal loss in AD patients. Large multicenter trials are currently underway with nerve growth factors (compounds that promote growth, survival, and regeneration of neurons), as well as drugs such as memantine. However, the key event that will provide direction for cure would be a full understanding of AD etiology.

The potential usefulness of hormone replacement, anti-inflammatory drugs, and Ginkgo biloba extract for the prevention of AD is currently being studied. Further information about these studies is available from the Alzheimer’s Disease Education and Referral Center of the National Institutes of Health (http://www.alzheimers.org/ir.html or 800-438-4380). These and other promising areas of investigation bring hope that in the near future we will be able to turn our attention from the palliative treatment of AD to primary prevention, or at least to delaying the progression of the disease to its most disabling stages.

Research Involving Genetics of AD

A 30-year-old woman with a genetic disorder linked to early onset of AD has become the first to successfully undergo in vitro fertilization with preimplantation genetic diagnosis (PGD) of the embryos to avoid passing the defect on to her children (217). PGD, prenatal diagnosis, preimplantation embryo selection, and presymptomatic testing has been offered to families of patients who have early-onset familial AD. Complex legal and ethical issues surrounding these interventions need to be addressed before these interventions can be routinely recommended. There is great potential for stem cell treatment of patients with AD, but ethical issues will need to be addressed before fetal stem cell research can be carried out.

Surgical Interventions

Low-flow cerebrospinal fluid (CSF) drainage using a shunt is a recent surgical intervention that was found to be relatively safe in the treatment of patients with AD (218). The shunt is implanted in the lateral ventricle of the brain, from which point it empties CSF into the peritoneal cavity. The theory is that poor circulation of the CSF is contributing to AD by allowing the deposition of amyloid and or other toxins. The study also found promising results in 12 patients: either a 3-month improvement or stabilization. A larger, randomized, double-blind, controlled clinical trial is underway to elucidate the potential for this intervention in the treatment of AD.

Summary and Conclusions

AD is one of the principal causes of disability and decreased quality of life among the elderly and is a leading obstacle to successful aging. AD is a treatable condition. Today’s treatment options are greatly improved over those available a few years ago. The complexity and heterogeneity of AD requires comprehensive assessment and possibly multiple layers of intervention for the patient as well as the caregiver. Current management focuses on establishing an early accurate clinical diagnosis, early institution of ChEIs, treating medical comorbidities and dementia-related complications, ensuring appropriate services are provided, supporting caregivers, and treating cognitive and behavioral problems and functional deficits with appropriate non-pharmacological and pharmacologic interventions. A therapeutic alliance between physician and caregiver is critical to the success of AD management. AD is a terminal illness, and the patients and caregivers should be given an early opportunity to decide about intensity of care before the disease inevitably progresses. Physician involvement in ethical issues raised in the management of AD and a multidisciplinary team approach is strongly recommended.

ChEIs should be considered in all patients with mild to moderate AD. ChEIs have been shown to temporarily stabilize cognition and ADL and may delay nursing home placement and reduce demands on caregiver time. Preliminary evidence also indicates that these benefits may extend to patients with more advanced AD and rapidly progressive AD as well as to patients with VaD and LBD. Patients not responding to one agent in the class may respond to another. Discontinuation should be monitored; deterioration during withdrawal indicates therapeutic benefit and the medication should be reinstated. Other drugs such as memantine look promising in their effect in slowing functional decline in patients with moderate to severe AD. Estrogen should not be prescribed to treat AD.

Psychotropics play a critical role in the management of moderate to severe behavioral disturbances in patients with AD. Short-term programs directed toward educating family caregivers about AD should be offered to improve caregiver satisfaction. Intensive long-term education and support services (when available) should be offered to caregivers of patients with AD to delay time to nursing home placement. Professional caregivers need higher expectations and better training and support. Staff of long-term care facilities should receive education about AD to reduce the use of unnecessary psychotropics. This article is by no means exhaustive. Readers are encouraged to read other articles for treatment of problems/issues that we may not have adequately addressed in the management of AD (Table 9).
Patients with AD are at risk of becoming medical orphans in a health system geared toward cure and in a culture where it is “normal” for the elderly to suffer. AD patients and their families have a right to receive competent, compassionate, and consistent care. With appropriate treatment, we can substantially reduce the number of AD patients receiving inappropriate medication, futile procedures, and hospitalization and surgeries.

With active research in AD, some of the current recommendations may become outdated by the time of publication of this article. Also, physicians must decide to adopt any particular recommendation in the light of available resources and the circumstances of individual patients.

Patients and their families have reason to be optimistic. The intense ongoing research in the area of etiology and treatment of AD offers hope and confidence that treatments to delay onset of AD; to treat, inhibit, and reverse symptoms; and, ultimately, to prevent AD, will indeed be discovered. Until then, patients and families can benefit from the variety of pharmacologic and nonpharmacologic interventions described here.

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REFERENCES


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