CLINICAL REVIEW

Guidelines for the Management of Cognitive and Behavioral Problems in Dementia

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Family physicians play a crucial role in the management and ongoing care of patients with Alzheimer disease (AD). This article reviews the effects of nonpharmacologic and pharmacologic interventions on the functional abilities and behavior of patients with dementia and how these can be implemented into clinical practice. Nonpharmacologic interventions are recommended as the initial strategy for managing problematic behaviors. Strategies for improving behavior include ensuring that the patient's environment is safe, calm, and predictable; removing environmental stressors; and identifying and avoiding situations that agitate or frighten the patient. Simple interventions include redirecting and refocusing the patient, increasing social interaction, establishing regular sleep habits, eliminating sources of conflict and frustration, and establishing rewards for successes. The effectiveness of long-term behavioral management is largely dependent on the caregiver; as such, it is important to assess the role and needs of the caregiver.

Because currently available therapies cannot reverse the pathologic processes of AD, the primary objective of pharmacotherapy is to preserve cognitive and functional ability, minimize behavioral disturbances, and slow disease progression. Cholinesterase inhibitors represent first-line therapy for patients with mild to moderate AD, whereas a glutamate *N*-methyl *D*-aspartate antagonist is used in the treatment of moderate to severe AD. Looking forward, there are a number of therapies in development aimed at modifying the disease course; these include amyloid-lowering drugs, τ-based and neuroprotective approaches, acetylcholine agonists, and mitochondrial inhibitors. (J Am Board Fam Med 2012; 25:350–366.)

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The Role of the Family Physician in Treating Dementia

Primary care is the point of first medical contact for people with dementia and hence the cornerstone of ensuring early detection, timely intervention, and effective ongoing management.[1] Inadequate detection and poor management have been reported globally,[2,3] leading to people with dementia and their families being denied optimal pharmacologic[4] and psychosocial intervention.[5] Alzheimer disease (AD), the most common cause of dementia worldwide, is a complex disorder that warrants a multidimensional approach with regular monitoring of the patient for increasing cognitive, functional, and behavioral challenges. Management consists of both pharmacologic and nonpharmacologic interventions as well as referrals to social service agencies and support resources, such as the Alzheimer's Association (www.alz.org). The family physician

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plays a key role in linking the family to community resources and other health care and social service providers who will help implement the overall care plan.[6,7] Physicians also play a key role in coordinating the invaluable support network of nurse practitioners, physician assistants, social workers, and medical assistants. Moreover, the family physician can assist in maintaining the physical health of patients with dementia, for example, assisting with the evaluation and treatment of visual and hearing defects, which are more common with aging. Such assistance can help directly and indirectly in the management of dementia.

For the purpose of this review, an electronic search of English-language articles (without time limits) was performed using PubMed and MEDLINE. The primary research parameters were *Alzheimer's disease*, *diagnosis*, *therapy*, *treatment*, and *therapeutic*. Original research articles, reviews, and other articles of interest were reviewed, and the most important information was identified. This review provides a summary of these findings as well as practical advice for the busy clinician.

Managing Cognitive, Memory, and Functioning Problems

Goals of Therapy and Likely Outcomes

The management of a patient with AD is a complex and evolving task because the natural history of AD is one of progressive decline; patients' cognitive, physical, and social functions gradually deteriorate.[8] One of the key aspects of optimal management of dementia is realistic expectations for therapeutic outcomes, including treatment effects and potential outcomes; it is, therefore, imperative that the family physician is aware of these issues and discusses them with both the patient and caregiver.[9] To be effective, interventions for patients with dementia ideally will improve functional status to a level that is detectable by caregivers or health care providers.

In clinical trials, the Alzheimer's Disease Assessment Scale, Cognitive Subscale (ADAS-Cog), a 20-minute, 11-item, 70-point scale that tests memory, language, orientation, and praxis, is often used to determine rate of cognitive decline. The total score ranges from 0 to 70, with a high score indicating greater impairment.[10,11] Because of the progressive nature of AD, there may be brief plateaus during the illness; however, the decline is fairly consistent, tending to increase or accelerate as patients enter the moderate stage.[12] Therefore, any "improvement" from an intervention for dementia must take this into account. As such, "improvement" can be defined as a reduction in rate of decline.[8] For example, patients with mild dementia experience an average rate of decline of ≤5 ADAS-Cog points,[8] and slowing this decline by 2 to 3 ADAS-Cog points over a year could mean a delay of up to 7 months in disease progression. In contrast, patients with moderate dementia (ADAS-Cog score >15 but <55) experience an average decline in cognition of 7 to 11 ADAS-Cog points (2–4 Mini Mental State Examination [MMSE] points) annually.[13] Therefore, for people with moderate dementia, slowing decline by 2 to 3 ADAS-Cog points per year could mean a delay of 2 to 5 months in disease progression. In general, cholinesterase inhibitors (ChEIs) do not delay ultimate progression of AD by more than 6 to 7 months.

Nonpharmacologic Interventions

An increasing number of nonpharmacologic therapies are now available for people with dementia, including behavioral therapy, reality orientation, art therapy, music therapy, complementary therapy, aromatherapy and bright-light therapy, as well as cognitive behavioral therapies. There are several areas of overlap between these therapies and each approach is rarely used in isolation[14]; it is therefore useful for clinicians to be familiar with several of these approaches to enable a combination of treatments to be tailored to individual requirements.[15] Therapy is now directed toward person-centered forms of care and greater attempts are made to understand the individual's experience of dementia and to employ strategies to improve the person's quality of life (QoL).[15] Individualized nonpharmacologic interventions include self-affirming exercises, such as reminiscence therapy, and structured socialization, such as pet therapy and viewing family videotapes.[16] The efficacy of these interventions has been demonstrated in both small and larger studies.[17]

Dietary Supplements

Several nutrient deficiencies are known to be risk factors for AD. Evidence suggests that consumption of fish with high fat content and marine omega-3 polyunsaturated fatty acid decreases the risk of cognitive impairment and dementia.[18] It is, therefore, not unusual in clinical practice to encounter patients and caregivers inquiring about dietary recommendations for lowering the risk of dementia. However, to date, there are no clinical trials to support a recommendation of dietary and supplemental omega-3 polyunsat-

urated fatty acid for the sole purpose of preventing cognitive impairment or dementia.[18] Nevertheless, it is not unwarranted to encourage adequate consumption of fatty fish as part of general dietary recommendations that may also confer benefits of reducing the risk of stroke and heart disease.[19]

There has been recent attention regarding the health benefits of curcumin (found in the commonly used Asian spice, turmeric) in AD. In animal studies, low-dose curcumin effectively disaggregates β-amyloid and prevents fibril and oligomer formation, supporting the rationale for curcumin use in clinical trials preventing or treating AD.[20] Indeed, a phase II clinical trial with patients with moderate to severe AD is ongoing, designed to determine whether curcumin can slow cognitive deterioration.[21]

Finally, recent studies from both the United States and Europe have suggested that vitamin D deficiency may be associated with increased odds of cognitive impairment in older persons.[22,23] Indeed, results from a study in the United States in which cognitive impairment was assessed using measures of immediate and delayed verbal memory, orientation, and attention reported a link between vitamin D deficiency and cognitive impairment in 3325 adults aged >65 years.[22] The multivariate adjusted odds ratios (95% confidence interval) of cognitive impairment in patients who were vitamin D insufficient (≥50 < 75 nmol/L), deficient (≥25 < 50 nmol/L), and severely deficient (<25 nmol/L) compared with those sufficient (≥75 nmol/L) were 0.9 (0.6–1.3), 1.4 (1.0–2.1), and 3.9 (1.5–10.4), respectively (*P* for linear trend = .02), suggesting that vitamin D deficiency is associated with increased odds of cognitive impairment among the elderly population. Similar findings also have been reported in a European study.[23] Although further exploration of a possible causal relationship between vitamin D deficiency and cognitive impairment is warranted, these findings raise important new possibilities for treatment and prevention of cognitive decline in patients with AD.

Medical Foods

Medical foods as a class of intervention alternatives are not well known to most clinicians but are a growing area. Medical foods are a special category of US Food and Drug Administration (FDA)–regulated agents intended to provide specific nutritional requirements for patients with certain diseases; they can, therefore, provide an additional supplement in a comprehensive therapeutic regimen for patients with AD. Products being marketed currently or developed in the United States for the management of dementia include Caprylic triglyceride (Axona, Accera, Inc., Broomfield, CO) and Souvenaid (Nutricia Advanced Medical Nutrition, Schiphol, The Netherlands).

Axona has been developed for the clinical dietary management of the metabolic processes associated with mild to moderate AD. It is a formulation of caprylic triglyceride, a medium-chain triglyceride that is metabolized to ketone bodies, predominantly β-hydroxybutyrate, a common metabolic substrate that is produced normally by the body for neurons in starvation states where glucose is less available.[24] A double-blind crossover study conducted in patients with AD or mild cognitive impairment demonstrated that Axona therapy was associated with significant improvements in ADAS-Cog; however, the effect was seen only in patients who were not carriers of apolipoprotein E ε4.[24] Similar results were reported in a 90-day, randomized, placebo-controlled study in patients with mild to moderate AD.[25] Significant gastrointestinal side effects have been associated with Axona, and slow titration of the product is being recommended.

Souvenaid (food) combines omega-3 fatty acids, choline, uridine monophosphate, and a mixture of antioxidants and B vitamins.[26] In a randomized, controlled trial involving more than 200 patients with mild AD, Souvenaid was well tolerated and improved memory compared with placebo.[27]

Pharmacologic Interventions

There are currently no means of reversing the pathologic processes of AD. Currently available medications do not halt the underlying degenerative process but can slow disease progression and therefore delay symptomatic decline.[28] The specific goals of therapy are to preserve cognitive and functional ability, minimize behavioral disturbances, and slow disease progression with maintenance of patients' and caregivers' QoL.[29] Nevertheless, realistic expectations of treatment outcomes are needed because the impact for most patients is likely to be modest and temporary, with not every patient responding to treatment. The main benefit of pharmacotherapy is an attenuation of decline over time rather than an improvement in cognitive or behavioral symptoms. It is important to discuss this point with patients and their families, who may

expect improvement rather than relative stability.[30] Failure to do so often will result in patient and family dissatisfaction with prescribed therapies and the risk of discontinuation. Beneficial response to a ChEI (ie, delayed deterioration of cognitive or behavioral problems) can be determined from the physician's global assessment of the patient, the primary caregiver's report, a neuropsychologic assessment or mental status questionnaire, or evidence of behavioral or functional changes.[7]

Four drugs are commonly used for treating AD: 3 ChEIs approved for mild to moderate disease, one of which also is approved for severe AD, and a glutamate *N*-methyl *D*-aspartate (NMDA) antagonist approved for moderate to severe disease (Table 1).[30]

Mild to Moderate Disease

Since the introduction of the first ChEI in 1997, most clinicians would consider these agents to be first-line pharmacotherapy for mild to moderate AD.[11] Four ChEIs are currently available: tacrine (Cognex, Shionogi, Inc., Atlanta, GA); donepezil (Aricept, Eisai Co, Ltd., Woodcliff Lake, NJ); rivastigmine (Exelon, Novartis Pharmaceuticals Corp., East Hanover, NJ); and galantamine (Reminyl, Ortho-McNeil Neurologics, Titusville, NJ). Tacrine is not commonly used because of a poor tolerability profile and low oral bioavailability, and it is, therefore, excluded from this discussion.[31] ChEIs raise acetylcholine levels in the brain by inhibiting acetylcholinesterase.[6] Despite minor variations in their mode of action there is no evidence to suggest any difference in efficacy between the 3 commonly used ChEIs.[11] Likewise, the tolerability profile is similar between the ChEIs for the oral formulations. However, the 10-cm^2 rivastigmine patch has shown efficacy similar to oral rivastigmine formulations, but with approximately two-thirds fewer reports of nausea and vomiting, with adverse event (AE) rates similar to those of placebo[32] (Table 1). AD often is accompanied and worsened by malnutrition, and weight loss is a frequent complication of AD, occurring in approximately 40% of patients at all stages.[33] Donepezil, rivastigmine, and galantamine cause a broad spectrum of AEs, of which nausea, vomiting, diarrhea, and weight loss are the most common.[34,35]

There continues to be debate regarding the extent of the benefits achieved with ChEIs. Although some assert that the most that can be achieved with ChEIs is symptom modification,[11] others consider these agents to have disease-modifying effects.[36] In one study, after discontinuation of therapy, rivastigmine-treated patients showed less deterioration in cognitive function compared with placebo-treated patients, suggesting an effect on disease progression.[37] In another study, donepezil treatment slowed progression of hippocampal atrophy compared with untreated patients, suggesting a neuroprotective effect of donepezil in AD.[38] However, these early observations require confirmation, and, at present, the ChEIs generally are considered symptomatic medications.

A systematic analysis of double-blind, placebo-controlled trials of ChEIs demonstrated treatment effects ranging from a 1.4- to 3.9-point improvement at 6 months and 1 year, in the midrange of the 70-point ADAS-Cog scale.[11] In clinical trials, a change of 4 points is considered clinically significant for patients with mild to moderate dementia.[39,40] As such, the symptomatic improvements observed are modest and of debatable clinical significance, despite being statistically significant.[35] In a meta-analysis of 16 double-blind, placebo-controlled trials of ChEIs composed of almost 8000 patients, the numbers needed to treat for one additional patient to benefit were 7 for stabilization or better, 12 for minimal improvement or better, and 42 for marked improvement.[41] Although the numbers needed to treat seem favorable, uncertainty remains regarding the clinical relevance of these outcomes and the duration of the apparent benefit because the majority of trials reviewed were of less than 26 weeks' duration.

In addition to their effects on cognition, these agents also have demonstrated beneficial effects on measures of behavior, activities of daily living (ADLs), and global patient function. A recent meta-analysis that analyzed clinical results from 29 randomized, placebo-controlled trials of patients with mild to moderate AD found that ChEI therapy was associated with significant modest benefits in terms of neuropsychiatric and functional outcomes.[42] Current guidelines acknowledge that preventing or delaying further loss of ADL function is an important goal of AD therapy[43] and that the benefits of ChEIs may be diminished when treatment is delayed.[28] Significant preservation of ADL function has been observed with donepezil, galantamine, and rivastigmine compared with placebo.[29]

ChEIs also have been shown to reduce AD caregiver burden: in patients with moderate to severe

Table 1. Cholinesterase Inhibitors and Memantine for the Treatment of Cognitive Deficits in Patients with Alzheimer Disease (AD)[6,59]

Drug	Approved Indication	Suggested Dosage	Side Effects	Additional Notes/Caution
Cholinesterase inhibitors				
Donepezil (Aricept)	Mild to moderate AD Severe AD	Once daily, beginning with 5 mg/day, which can be increased to 10 mg/day (maximum dosage) after 4 weeks	AEs are mild and include nausea, vomiting, and diarrhea	Gastrointestinal-related AEs can be reduced if medication taken with food Some patients exhibit an initial increase in agitation, which subsides after first few weeks of therapy
Rivastigmine (Exelon)	Mild to moderate AD	*Oral*: Twice daily, beginning with 1.5 mg *Transdermal patch*: Once daily, 4.6 or 9.5 mg The target dose is 9.5 mg/24 hr per patch (a 10 cm^2 patch) and requires a simple one-step dose titration to the therapeutic dose There is a higher-dose patch (20 cm^2) available, delivering 17.4 mg/24 hr; however, it is currently an unapproved treatment in the United States. Lack of approval was based on it having similar efficacy to the 10 cm^2 patch, but with a tolerability profile comparable to that of the capsule formulation	AEs include nausea, vomiting, diarrhea, weight loss, headaches, abdominal pain, fatigue, anxiety, and agitation Gastrointestinal-related AEs are less prominent with the patch: the 9.5 mg/24 hr patch provides efficacy similar to that of the highest dose of capsules, with 3 times fewer reports of nausea and vomiting	Higher dosages are more efficacious than lower dosages No laboratory monitoring is required
Galantamine (Razadyne)	Mild to moderate AD	Twice daily, beginning with 4 mg After 4 weeks, dosage is increased to 8 mg twice daily An increase to 12 mg twice daily can be considered on an individual basis after assessment of clinical benefit and tolerability Also available in an extended-release formulation that can be taken once daily	Most common side effects are nausea, vomiting, and diarrhea	Gastrointestinal-related AEs can be minimized by titrating the dosage gradually and taking the medication with meals
NMDA antagonist				
Memantine (Namenda)	Moderate to severe AD	Twice daily, beginning with 5 mg, increasing the dose to 10 mg twice daily over 3 weeks	AEs include fatigue, pain, hypertension, headache, constipation, vomiting, back pain, somnolence, dizziness	Moderate to severe AD may respond better with memantine/donepezil combination versus donepezil alone

AE, adverse event; NMDA, *N*-methyl *D*-aspartate.

AD, donepezil treatment for 24 weeks significantly reduced caregiver time spent assisting patients with basic and instrumental ADLs (−52 minutes/day; $P < .005$).[44] A small study has demonstrated that rivastigmine treatment reduces caregiver time spent assisting with ADLs (up to 690 hours over 2 years).[45] Longer periods of treatment with ChEIs also decrease the risk for nursing home placement.[46,47] A retrospective analysis of a large US medical claims database showed that over a 27-month follow-up period, more patients who were not treated with ChEIs were placed in nursing homes (11.0%) than were those who received either rivastigmine (3.7%) or donepezil (4.4%).[47] These studies suggest that ChEIs enable patients to live longer in community settings with associated personal, social, and economic benefits.[29]

Memantine (Namenda, Forest Pharmaceuticals, St. Louis, MO) is sometimes used to treat patients with less severe disease, despite its use in early AD not being supported by the FDA. Although memantine has been reported to improve cognition, global status, and behavior in patients with mild to moderate AD,[48] its mechanism of action would suggest that it does not have a place in early AD. Memantine is not a ChEI; it is a low- to moderate-affinity, noncompetitive (channel blocking), NMDA-receptor antagonist that seems to block pathologic neural toxicity associated with prolonged glutamate release.[49] Blockade of NMDA receptors by memantine could confer disease-modifying activity in AD by inhibiting the "weak" NMDA receptor–dependent excitotoxicity that contributes to the neuronal loss underlying the progression of dementia.[49] As such, memantine is not effective until weakened neurons become vulnerable to glutamate-induced excitotoxicity, and therefore it cannot substitute for ChEIs because of its inability to enhance cholinergic neurotransmission required for memory and learning.[49]

Moderate to Severe Disease

Memantine is approved for the treatment of moderate to severe AD on the basis of a study in which patients with moderate to severe AD who received 20 mg memantine monotherapy showed less decline in cognition and function while maintaining good tolerability after 6 months compared with those who received placebo.[50] The ChEI donepezil also recently has been approved for use in severe AD.

Recently, donepezil 23 mg/day has been approved for the treatment of moderate to severe AD. Results from a 24-week, randomized, double-blind study reported that donepezil 23 mg/day was associated with greater benefits in cognition (as assessed by the Severe Impairment Battery) compared with donepezil 10 mg/day, although the between-treatment difference in the Clinician's Interview-Based Impression of Change plus Caregiver Input Scale was not significant. The most commonly reported side effects with donepezil 23 mg/day were nausea vomiting, and diarrhea, which occurred at a higher incidence than with donepezil 10 mg/day.[51]

Combination therapy of a ChEI and memantine is rational from a pharmacologic perspective because the agents have different mechanisms of action. In a randomized controlled trial, patients with moderate to severe AD who were already receiving donepezil derived significant benefit from the addition of memantine in terms of cognition, ADLs, global outcome, and behavior.[52] There are also economic benefits associated with the addition of memantine to donepezil treatment for patients with advanced AD. A recent study demonstrated improvement in clinical outcomes plus cost savings associated with the use of memantine.[53] In a study by Tariot et al,[52] the incidence of nausea was substantially lower in patients receiving memantine add-on therapy compared with those receiving donepezil monotherapy. The safety and tolerability of combining rivastigmine capsule and memantine also has been studied in a 26-week, prospective, open-label study of patients with moderate AD.[54] The combination was found to be both tolerable and safe, with a reduced incidence of gastrointestinal-related AEs compared with those documented in the US prescribing information for rivastigmine, suggesting that this beneficial effect of memantine may be applicable across ChEIs.[54]

Adjuncts to Pharmacotherapy for Improving Cognitive Function

A recent study has demonstrated that ChEI-treated patients with early AD who received psychosocial support plus cognitive-motor intervention (CMI) had additional mood and cognitive benefits over those experienced by ChEI-treated patients who received psychosocial support alone. The CMI consisted of a 1-year structured program of 103 sessions, including reality orientation techniques, cognitive exercises, training of ADLs, and psychomotor exercises. Cognitive exercises were designed to stimulate memory, attention, language,

visuospatial abilities, calculation, and frontal/executive functions. The ADL training was related to the particular cognitive function stimulated at each session (eg, money handling was trained after calculation exercises). The results showed that patients in the CMI group maintained cognitive status at 6 months, whereas patients in the control group had significantly declined by that time. In addition, more patients who received CMI maintained or improved their affective status after 1 year (CMI group, 75%; control group, 47%).[55]

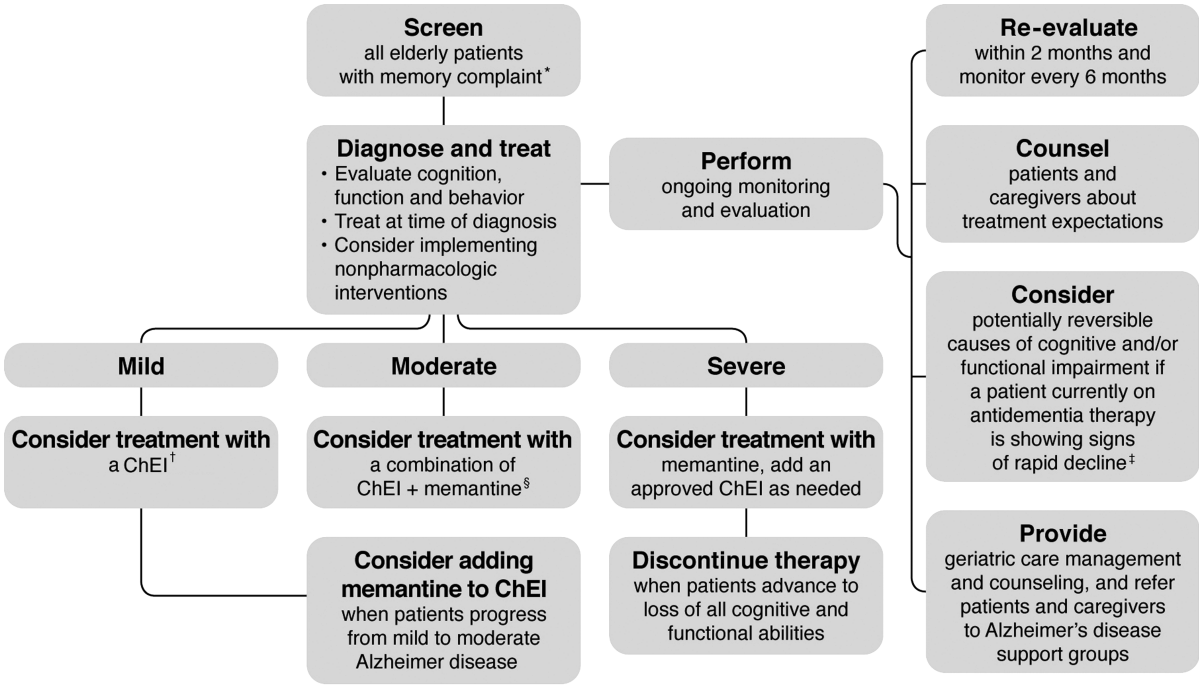
Treatment Guidelines

In 2006, a panel of leading experts published recommendations for best practice in the treatment and management of AD. These recommendations were developed in an effort to address issues surrounding early diagnosis, treatment, and care management of AD, as well as societal and managed-care implications.[56] An algorithm was created to assist providers with the appropriate utilization of therapy and care management (Figure 1). This algorithm recommends initiating ChEI therapy in patients with mild AD and using combination therapy with a ChEI and memantine for patients who progress from mild to moderate AD. Alternatively, global guidelines recommend that patients who continue on the drug should be reviewed every 6 months by MMSE score and global, functional, and behavioral assessment.[9] Treatment should be continued only while the patient's MMSE score remains ≥10 points and their global, functional, and behavioral condition indicates that the drug is having a worthwhile effect. In patients with moderate to severe AD (MMSE score <12), treatment with memantine can be considered, alone or in combination with a ChEI.[9]

Managing Mood Disorders and Behavior Problems

Traditionally, cognitive function has been the main focus of interest in treatment and research of peo-

Figure 1. Treatment and management of Alzheimer disease. *Memory complaint may be raised by family or caregiver. All patients aged ≥75 years should be screened regardless of clinical presentation. †Cholinesterase inhibitors (ChEIs) are included for mild to moderate Alzheimer disease, excluding donepezil, which is indicated for mild, moderate, and severe Alzheimer disease. ‡Possible causes include medical comorbidities, the effects of other drugs, behavioral disturbances, or delirium. §Memantine is indicated for the treatment of moderate to severe Alzheimer disease. (This treatment algorithm is derived from recommendations published in Ref. 56. Reproduced with permission from RG Stefanacci. Reinforcing the value of combination therapy to treat moderate to severe alzheimer's disease. Phys Week 2009;26(9). © 2009 Physician's Weekly, LLC.)



ple with dementia. It is becoming increasingly recognized, however, that noncognitive symptoms are those that are most disturbing to families and caregivers and may seriously impact not only the patient's well-being, but also the family's, caregivers', and providers' approaches to managing the patient.[15] The most common symptoms are agitation, aggression, mood disorders/behavioral disturbance, apathy, depression, psychosis and hallucinations, with sexual disinhibition, elation/euphoria, appetite and eating disturbances, and abnormal vocalizations occurring less frequently.[15,57] These have been grouped together under the umbrella term *behavioral and psychological symptoms of dementia* by the International Psychogeriatric Association.[58] As the disease progresses, these symptoms become predominant problems[59] and impose an enormous toll, both emotionally and financially.[17] They are also a common reason for institutionalization of people with dementia and they increase the burden and stress of caregivers.[55,57,60]

Nonpharmacologic Interventions

Nonpharmacologic interventions are recommended as the most appropriate initial strategy for managing inappropriate behaviors in dementia because (1) they address the psychosocial/environmental underlying reason for the behavior, and (2) they avoid the limitations of pharmacologic interventions, namely, adverse side effects, drug–drug interactions, and limited efficacy.[15,17,61] Increased involvement of caregivers often has a secondary benefit of providing overburdened caregivers with an opportunity to receive support, information, and skills. Furthermore, environmental factors (eg, confusing or noisy surroundings) or interpersonal factors (eg, arguing with the patient) are often the primary triggers of behavior problems. Attention to these factors through nonpharmacologic approaches can be effective in alleviating or preventing behavioral problems in individuals with dementia and should be considered first.[6,59,61] A recent consensus statement recommended that all treatment approaches start with rigorous attempts to identify any reversible causes of these behaviors and alleviate these factors[16] by modifying the physical and interpersonal environments.[62,63] Common triggers of agitation and aggression include pain, fecal impaction, medical illness, boredom, loneliness, depression, and social and environmental stressors. Unfortunately, in practice, pharmacologic approaches involving neuroleptic or other sedative medication are often used as the first-line treatment, despite the modest evidence of efficacy from clinical trials in which high placebo response rates frequently are seen.[15,64]

Patients with AD function best in an environment that is safe, calm, and predictable, and their caregivers require ongoing support and education to develop realistic expectations throughout the course of the illness.[30] Caregivers can be taught strategies to reduce agitation and anxiety in patients with dementia.[65] One such strategy utilizes the 3 Rs approach (***r***epeat, ***r***eassure, and ***r***edirect), whereby the caregiver repeats an instruction or answer to a question as needed and redirects the patient to another activity to divert attention from a problematic situation. A predictable routine also is important and may avert certain behavioral problems. For example, scheduled toileting or prompted voiding can reduce urinary incontinence.[6] Training programs for family caregivers of people with dementia, such as Savvy Caregiver, Staff Training in Assisted-Living Residences Caregivers, and Resources for Enhancing Alzheimer's Caregiver Health, have resulted in decreased agitation among people with dementia who live at home and reduced feelings of burden and depression among family caregivers.[66–69]

Nonpharmacologic interventions can be as simple as redirecting and refocusing the patient, increasing social interaction, initiating enjoyable activities, establishing regular sleep habits, eliminating sources of conflict and frustration (eg, activities that the patient can no longer undertake), and establishing rewards for successes, however small (Table 2).[61] The principles of person-centered care, which aims to treat people as unique individuals with their own personality and preferences, are essential in the nonpharmacologic management of individuals with AD.[17] For example, a person's religious background may influence his or her behavior. Patients of certain faiths may become agitated during intimate situations, such as bathing or dressing, when in the presence of caregivers who are of the opposite sex; a caregiver of the same sex may lead to improvement in behavior. The removal of any triggers of behavioral problems or the provision of comforting stimulation, such as the patient's favorite music, also may be beneficial.[70]

The use of behavioral interventions in dementia is hindered by the fact that the patient's cognitive functioning is declining progressively. As such, the

Table 2. Nonpharmacologic Interventions for Reducing Behavioral Disturbances in Alzheimer Disease (AD)[6,95]

Symptom	Response
Indecisiveness	• Reduce choices
Disorientation	• Provide the patient with a predictable routine (eg, exercise, meals, and bedtime should be routine and punctual) • Avoid relocation; if necessary bring familiar items • Allow the patient to dress in his or her own clothing and keep possessions • Use calendars, clocks, labels, and newspapers for orientation to time • Use color-coded or graphic labels (eg, on closets, table service, drawers) as cues for orientation in the home environment
Hallucinations	• Do not be overly concerned if they are not distressing to the patient • Consider antipsychotic agents where necessary, but fully inform family and caregivers of the risks/benefits of these medications
Delusions	• Redirect and distract the patient • Consider using antipsychotic medications
Repetitiveness	• Answer decisively, then distract
Lack of motivation	• Ensure tasks are simple so that the patient can complete them; break up complex tasks into smaller steps • Before performing all procedures and activities, explain them to the patient in simple language
Wandering (usually occurs later in the disease, ie, moderate to severe AD)	• Register the patient in the Alzheimer's Association Safe Return Program • Secure the environment with complex handles • Equip doors and gates with safety locks • Inform neighbors
Agitation	• Use distraction and redirection of activities to divert the patient from problematic situations • Reduce excess stimulation and outings to crowded places (overexposure to environmental stimuli can lead to agitation and disorientation) • Use lighting to reduce confusion and restlessness at night • Avoid glare from windows and mirrors, noise from a television, and household clutter
Accident-prone	• Provide a safe environment (eg, no sharp-edged furniture, no slippery floors or throw rugs, no obtrusive electrical cords) • Install grab bars by the toilet and in the shower
Ensure that comorbid conditions are optimally treated	
Consider using a day care program for patients with AD	

effects of interventions must be monitored continually and adjustments made over time in response to new behaviors that may emerge.[62] In patients with disruptive and hard-to-treat behavioral problems, referral to a behavioral specialist such as a geriatric psychiatrist should be considered.

Cognitive Behavioral Therapy

Over the past 10 years there has been an increasing interest in applying therapeutic frameworks, such as cognitive behavioral therapy (CBT), cognitive stimulation therapy (CST), and interpersonal therapy to dementia. These therapies are designed to actively stimulate and engage people with dementia; group therapy, such as that used for CST, provides an optimal learning environment and the social benefits of a group and aims to create an environment in which people learn and strengthen their existing resources. The principles of person-centered care are essential when delivering CST for individuals with dementia; as such, group members often are assigned a role within the group according to their interests and abilities. During each themed session, there is a range of activities available, which allows the facilitator to adapt the level of difficulty of the activities depending on the group's cognitive capabilities, interests, and gender mix; each individual can be provided with an activity suitable for him or her personally. Sessions for CST include physical games, sound and word association, and faces/scenes. Individuals are asked to give their opinions rather than provide factual answers, and multisensory stimulation is used when possible. Teri and Gallagher-Thompson[71] reported positive findings from a clinical trial of CBT with individuals with early AD, and individual and group CBT also has been used with some favorable results.[15,72] A CBT perspective is appropriate for

people with dementia because many of the behavioral difficulties encountered emerge through one or more of the following cognitive features: cognitive misinterpretations, biases, distortions, erroneous problem-solving strategies, and communication difficulties. Put simply, many of the challenges posed by people with dementia are caused by their thinking style—the very thing that is addressed in CBT. CBT, therefore, offers a framework within which to understand the individual's distressing experiences, and this understanding allows the clinician to target interventions more appropriately.[15]

Pharmacologic Interventions

Pharmacologic interventions are necessary when nonpharmacologic strategies fail to reduce behavioral symptoms sufficiently. Patients treated with ChEIs, memantine, or both may also experience behavioral benefits in terms of reduced severity of existing behavioral disturbances and fewer new behavior symptoms[29]; usually agitation/aggression and irritability show responsiveness to ChEIs, memantine, or both, whereas depression, apathy, and anxiety do not.

If behavioral disturbances persist despite the use of ChEIs, memantine, or both, a psychotropic agent may be necessary.[6] In accordance with the principles of geriatric psychiatry "start low and go slow, but go," the psychotropic agent should be initiated in a low dosage and then increased slowly until an adequate response occurs or side effects emerge. After behavioral disturbances have been controlled for 4 to 6 months, the dosage of the psychotropic agent can be reduced periodically to determine whether continued pharmacotherapy is required. The choice of psychopharmacologic agent is determined by specific target symptoms; some behaviors, such as wandering and pacing, are not amenable to drug therapy. Medications used to treat behavioral disturbances and mood disorders are summarized in Table 3.[6]

Atypical Antipsychotics

Atypical antipsychotic drugs have been commonly used off-label in clinical practice for treatment of serious, dementia-associated agitation and aggression, although they are not approved by the FDA for such use. In addition, these agents have a black-box warning of increased mortality among elderly patients with dementia-related psychosis. A meta-analysis assessed the evidence for increased mortality from atypical antipsychotic drug treatment for people with dementia. Fifteen trials (9 unpublished), generally 10 to 12 weeks in duration and including 16 contrasts of atypical antipsychotic drugs with placebo, met criteria for inclusion (aripiprazole [n = 3], olanzapine [n = 5], quetiapine [n = 3], risperidone [n = 5]; one trial was counted both as a risperidone trial and an olanzapine trial). A total of 3353 patients were randomized to study drug and 1757 were randomized to placebo. Results demonstrated that atypical antipsychotics may be associated with a 50% increased risk of death from all causes, which is similar to older antipsychotics, but there was no obvious difference in risk between the 4 agents.[73] In general, drugs may be used only when nonpharmacologic approaches have failed to control serious behavioral disruption adequately within 5 to 7 days.[16] Members of a recent consensus conference, who are experts in the field of geriatric mental health, reviewed the available evidence regarding the safety and efficacy of antipsychotic drugs. They concluded that problems in clinical trial design may have contributed to the negative results reported and suggested that future studies be required to address the benefit–risk balance in this patient population.[16] Nevertheless, the well-known incidence of side effects, such as sedation, falls, extrapyramidal signs, potential reduction in well-being and QoL,[14] and even possible acceleration of cognitive decline,[15,74,75] mean that the risk–benefit ratio must be considered carefully when prescribing these drugs to a generally frail population. If antipsychotics are indicated, then it is recommended that they are used at the lowest effective dose, with dosage reduced or treatment discontinuation considered on a regular basis.[59]

Agitation

Agitation and psychosis are distressing and are likely to overwhelm the caregiver's ability to cope. If behavioral and nonpharmacologic interventions are inadequate, mild agitation can be managed with low doses of medications, such as trazodone, carbamazepine, and valproate.[59] Tricyclic antidepressants and benzodiazepines generally are avoided in this population.[59] In patients with severe agitation and aggression, a recent consensus conference concluded that there is a need for an FDA-approved indication for treating dementia-related symptoms of severe and persistent or recurrent agitation and

Table 3. Pharmacologic Treatment of Behavior and Mood Disorders

Antipsychotic drugs		
Atypical antipsychotic agents		
Recommended uses: control of problematic delusions, hallucinations, severe psychomotor agitation, and combativeness		
General cautions: diminished risk of developing extrapyramidal symptoms and tardive dyskinesia compared with typical antipsychotic agents		
Warning: atypical antipsychotic agents can cause an increased risk of cerebrovascular events (including stroke) in elderly patients with dementia-related psychosis		
Risperidone (Risperdal)	Initial dosage: 0.25 mg/day at bedtime; maximum dosage: 2–3 mg/day, usually twice daily in divided doses	Comments: current research supports use of low dosages; extrapyramidal symptoms may occur at 2 mg/day
Olanzapine (Zyprexa)	Initial dosage: 2.5 mg/day at bedtime; maximum dosage: 10 mg/day, usually twice daily in divided doses	Comments: generally well tolerated
Quetiapine (Seroquel)	Initial dosage: 12.5 mg twice daily; maximum dosage: 200 mg twice daily	Comments: more sedating; beware of transient orthostasis
Typical antipsychotic agents		
Recommended uses: control of problematic delusions, hallucinations, severe psychomotor agitation, and combativeness; second-line therapy for patients who cannot tolerate or who do not respond to atypical antipsychotic agents		
General cautions: current research suggests that these drugs be avoided if possible because they are associated with significant, often severe side effects involving the cholinergic, cardiovascular, and extrapyramidal systems; there is also an inherent risk of irreversible tardive dyskinesia, which can develop in 50% of elderly patients after continuous use of typical antipsychotic agents for 2 years		
Warning: typical antipsychotic agents can cause an increased risk of cerebrovascular events (including stroke) in elderly patients with dementia-related psychosis		
Haloperidol (Haldol), fluphenazine (Prolixin), thiothixene (Navane)	Dosage: varies by agent	Comments: anticipated extrapyramidal symptoms; if these symptoms occur, decrease dosage or switch to another agent; avoid use of benztropine (Cogentin) or trihexyphenidyl (Artane)
Trifluoperazine (Stelazine), molindone (Moban), perfenazine (Trilafon), loxapine (Loxitane)	Dosage: varies by agent	Comments: agents with "in-between" side-effect profile
Mood-stabilizing (anti-agitation) drugs		
Recommended uses: control of problematic delusions, hallucinations, severe psychomotor agitation, and combativeness; useful alternatives to antipsychotic agents for control of severe agitated, repetitive, and combative behaviors		
General cautions: see comments about specific agents		
Trazodone (Desyrel)	Initial dosage: 25 mg/day; maximum dosage: 200 to 400 mg/day in divided doses	Comments: use with caution in patients with premature ventricular contractions
Carbamazepine (Tegretol)	Initial dosage: 100 mg twice daily; titrate to therapeutic blood level (4–8 μg/mL)	Comments: monitor complete blood cell count and liver enzyme levels regularly; carbamazepine has problematic side effects
Divalproex sodium (Depakote)	Initial dosage: 125 mg twice daily; titrate to therapeutic blood level (40–90 μg/mL)	Comments: generally better tolerated than other mood stabilizers; monitor liver enzyme levels; monitor platelets, prothrombin time, and partial thromboplastin time as indicated
Anxiolytic drugs		
Benzodiazepines		
Recommended uses: management of insomnia, anxiety and agitation		
General cautions: regular use can lead to tolerance, addiction, depression and cognitive impairment; paradoxic agitations occurs in about 10% of patients treated with benzodiazepines; infrequent, low doses of agents with a short half-life are least problematic		
Lorazepam (Ativan), oxazepam (Serax), temazepam (Restoril), zolpidem (Ambien), triazolam (Halcion)	Dosage: varies by agent	See general cautions

Continued

Table 3. Continued

Nonbenzodiazepines		
Buspirone (BuSpar)	Initial dosage: 5 mg twice daily; maximum dosage: 20 mg 3 times daily	Comments: useful only in patients with mild to moderate agitation; may take 2 to 4 weeks to become effective
Antidepressant drugs		
Recommended uses: see comments on specific agents		
General cautions: selection of an antidepressant is usually based on previous treatment response, tolerance and the advantage of potential side effects (eg, sedation vs activation); a full therapeutic trial requires 4–8 weeks; as a rule, dosage is increased using increments of initial dose every 5–7 days until therapeutic benefits or significant side effects become apparent; after 9 months, dosage reduction is used to reassess the need to medicate; discontinuing an antidepressant over 10–14 days limits withdrawal symptoms.		
Note: patients with depression and psychosis require concomitant antipsychotic medications.		
Tricyclic antidepressant agents		
Desipramine (Norpramin)	Initial dosage: 10–25 mg in the morning; maximum dosage: 150 mg in the morning	Comments: tends to be activating (eg, reduces apathy); lower risk for cardiotoxic, hypotensive and anticholinergic effects; may cause tachycardia; blood levels may be helpful
Nortriptyline (Pamelor)	Initial dosage: 10 mg at bedtime; anticipated dosage range: 10–40 mg/day (given twice daily)	Comments: tolerance profile is similar to that of desipramine, but nortriptyline tends to be more sedating; may be useful in patients with agitated depression and insomnia; therapeutic blood level "window" of 50–150 ng/mL (190–570 nmol/L)
Heterocyclic and noncyclic antidepressant agents		
Nefazodone (Serzone)	Initial dosage: 50 mg twice daily; maximum dosage: 150–300 mg twice daily	Comments: effective, especially in patients with associated anxiety; reduced dose of coadministered alprazolam (Xanax) or triazolam by 50%; monitor for hepatotoxicity
Buproprion (Wellbutrin)	Initial dosage: 37.5 mg every morning, then increase by 37.5 mg every 3 days; maximum dosage: 150 mg twice daily	Comments: activating; possible rapid improvement of energy level; should not be used in agitated patients and those with seizure disorders; to minimize risk of insomnia, give second dose before 3PM
Mirtazapine (Remeron)	Initial dosage: 7.5 mg at bedtime; maximum dosage: 30 mg at bedtime	Comments: potent and well tolerated; promotes sleep, appetite, and weight gain
SSRIs		
Recommended uses: may prolong half-life of other drugs by inhibiting various cytochrome P450 isoenzymes		
General cautions: typical side effects include sweating, tremors, nervousness, insomnia or somnolence, dizziness, and various gastrointestinal and sexual disturbances		
Fluoxetine (Prozac)	Initial dosage: 10 mg every other morning; maximum dosage: 20 mg every morning	Comments: activating, very long half-life; side effects may not manifest for a few weeks
Paroxetine (Paxil)	Initial dosage: 10 mg/day; maximum dosage: 40 mg/day (morning or evening)	Comments: less activating but more anticholinergic than other SSRIs
Sertraline (Zoloft)	Initial dosage: 25–50 mg/day; maximum dosage: 200 mg/day (morning or evening)	Comments: well tolerated; compared with other SSRIs, sertraline has less effect on metabolism of other medications
Citalopram (Celexa)	Initial dosage: 10 mg/day; maximum dosage: 40 mg/day	Comments: well tolerated; some patients experience nausea and sleep disturbances
Fluvoxamine (Luvox)	Initial dosage: 50 mg twice daily; maximum dosage: 150 mg twice daily	Comments: exercise caution when using fluvoxamine with alprazolam or triazolam

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SSRI, selective serotonin reuptake inhibitor.

aggression, even in the absence of psychosis.[16] Selective serotonin reuptake inhibitors seem to have efficacy for treatment of agitation in patients with AD. Studies have demonstrated benefits for agitation with citalopram compared with placebo[76] and similar efficacy compared with risperidone.[77]

Apathy

Apathy as a distinct psychiatric syndrome is an evolving concept but generally has been defined as poor initiation, impaired persistence, indifference, reduced emotional response, and low social engagement.[78] Although once believed to be just a symptom of depression, apathy is characterized primarily as a loss of motivation and reduced emotional reactivity, as opposed to depression, which is a mood disturbance.[79] Based on a limited but increasing body of evidence, methylphenidate seems to have some efficacy for the treatment of apathy in older adults with AD.[80]

Depression

Depression is common in older adults, including those with AD, and often is undiagnosed and untreated. The efficacy of antidepressants in patients with AD who also suffer depression has been demonstrated in clinical trial; the most useful medications are those with minimal anticholinergic side effects. Selective serotonin reuptake inhibitors, such as citalopram (Celexa, Forest Laboratories, Inc.) and sertraline (Zoloft, Pfizer, New York, NY), seem to be effective and have fewer side effects compared with other antidepressants; as such, they are considered the agents of choice for the treatment of depression in patients with dementia, although direct head-to-head studies have yet to be undertaken.[7,81]

The Needs of the Caregiver

Caregivers can become exhausted and frustrated; suffer depression, anxiety, and health problems; and be at increased risk of death.[2,9] Ideally, caregivers would receive assistance in caregiving, periodic assessment of their own health and welfare, support from family and friends, and respite care. One study has reported that the most consistently effective method of caregiver treatment interventions is to teach caregivers how to change or modify their interaction with the patient.[30]

Mittelman and colleagues[82] have demonstrated the effectiveness of long-term behavioral interventions for caregivers. Caregivers of patients with AD often suffer from depression, and optimizing long-term social support (individual and family counseling, the continuous availability of ad hoc counseling, and support group participation) can have a significant impact on depression in caregivers.[82] The same authors subsequently demonstrated that a program of counseling and support substantially increased the time spousal caregivers were able to care for AD patients at home. Patients whose spouses received the intervention experienced a 28% reduction in the rate of nursing home placement compared with usual care controls, with a difference in time to placement of 557 days. Improvements in caregivers' satisfaction with social support, response to patient behavior problems, and symptoms of depression collectively accounted for 61% of the intervention's beneficial impact on placement.[83,84] Furthermore, these benefits were greatest in patients who had only mild dementia, when nursing home placement is generally least appropriate.[83,84]

In the event that insufficient resources are available to provide for and protect both patient and caregiver, nursing home placement needs to be considered.[2] The progressive nature of dementia also must be emphasized, such that in the event of nursing home placement the caregiver does not consider it to be a failure on their part.[2] Discussing the benefits and disadvantages of institutional care with caregivers is often challenging. Although consideration of the patient's previously expressed wishes is essential, caregivers often feel constrained by comments made years earlier and believe that the patient would not accept long-term care. It can be helpful to remind caregivers that earlier comments were made without a full appreciation of the current circumstances and that expectations almost always change with chronic illnesses.[70]

Future Therapies

ChEIs and memantine are symptomatic therapies that help maintain neuronal function but do not have a significant impact on the underlying disease process. Their benefits are mild, and treatments that modify the disease course are urgently needed.[30,39] AD is the destruction of brain that cannot be regenerated, and any effective treatment

needs to start before much brain is destroyed. There recently has been intense research interest in characterizing the earliest stages of AD that precede the crossing of the dementia threshold, defined by functional disability.[85] Such preclinical disease detection may allow earlier therapeutic intervention before critical numbers of neurons are lost.

AD currently is thought to be a complex, multifactorial syndrome, unlikely to arise from a single causal factor; instead, a number of related biologic alterations are thought to contribute to its pathogenesis. In light of this, drug combinations that can act at different levels of the neurotoxic cascade offer new avenues toward curing AD and other neurodegenerative diseases.[86] Effective treatment will require attacking multiple targets.[87] At present, key therapeutic approaches include reduction of brain amyloid levels,[30,88,89] prevention of τ hyperphosphorylation into intraneuronal neurofibrillary tangles,[30,89] and stimulation of muscarinic acetylcholine receptors,[90,91] although novel therapies increasingly are targeted to preserving energy metabolism in the mitochondria.[92–94]

Conclusion

Family physicians play a crucial role in the care of patients with AD in terms of early detection, timely intervention, and effective ongoing management. Optimal management involves a multidimensional approach to treatment that includes the physician, geriatric care managers, social services, and the patient's family. The treatment of AD consists of both pharmacologic and nonpharmacologic interventions.

Nonpharmacologic interventions are recommended as the most appropriate initial strategy for managing problematic behaviors. Patients with AD function best in an environment that is safe, calm, and predictable. Interventions for improving behavior include reduction of environmental stressors and strategies to reduce the agitation and anxiety of the patient. These interventions can be as simple as redirecting and refocusing the patient, increasing social interaction, establishing regular sleep habits, eliminating sources of conflict and frustration, and establishing rewards for successes, however small. The role and needs of the caregiver are important, and the effectiveness of long-term behavioral interventions for caregivers has been demonstrated.

In the absence of means to reverse the pathologic processes of AD, the primary objectives of pharmacologic interventions are to preserve cognitive and functional ability, minimize behavioral disturbances, and slow disease progression. At present, four drugs are widely used to treat AD: 3 ChEIs, which are first-line treatment for patients with mild to moderate AD, and an NMDA antagonist approved for treatment of moderate to severe AD.

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