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A practical algorithm for managing Alzheimer's disease: what, when, and why?

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Abstract

Alzheimer's disease (AD) is the most common form of dementia and its prevalence is increasing. Recent developments in AD management provide improved ways of supporting patients and their caregivers throughout the disease continuum. Managing cardiovascular risk factors, maintaining an active lifestyle (with regular physical, mental and social activity) and following a Mediterranean diet appear to reduce AD risk and may slow cognitive decline. Pharmacologic therapy for AD should be initiated upon diagnosis. All of the currently available cholinesterase inhibitors (ChEIs; donepezil, galantamine, and rivastigmine) are indicated for mild-to-moderate AD. Donepezil (10 and 23 mg/day) and rivastigmine transdermal patch (13.3 mg/24 h) are indicated for moderate-to-severe AD. Memantine, an *N*-methyl-D-aspartate receptor antagonist, is approved for moderate-to-severe AD. ChEIs have been shown to improve cognitive function, global clinical status and patients' ability to perform activities of daily living. There is also evidence for reduction in emergence of behavioral symptoms with ChEI therapy. Treatment choice (e.g., oral vs. transdermal) should be based on patient or caregiver preference, ease of use, tolerability, and cost. Treatment should be individualized; patients can be switched from one ChEI to another if the initial agent is poorly tolerated or ineffective. Memantine may be introduced in moderate-to-severe disease stages. Clinicians will regularly monitor symptoms and behaviors, manage comorbidities, assess function, educate and help caregivers access information and support, evaluate patients' fitness to drive or own firearms, and provide advice about the need for legal and financial planning. Review of caregiver well-being and prompt referral for support is vital.

Introduction

Alzheimer's disease (AD) is the most common form of dementia, accounting for 60–80% of cases.¹ In the United States, one in nine people aged ≥ 65 years has AD (two-thirds of whom are women), and one person develops AD every 67 sec.¹ Alzheimer's Disease International estimates that the prevalence of AD will increase by 225% by 2050, affecting more than 115 million people globally,² and more than 13.8 million people in the United States.¹

AD is associated with initial memory loss, followed by impairments in cognitive function, language, visuospatial skills and executive function, coupled with behavioral changes.³ Terminally, patients may become bedridden,

incontinent and unable to communicate.⁴ AD imposes an intolerable burden on healthcare systems, society, patients and their families, and is one of the leading contributors to disability among elderly people.⁵ Most patients require assistance with activities of daily living (ADL), and many eventually require full-time care and supervision.^{2,4} Caring for a patient with AD can be stressful, especially if the patient displays neuropsychiatric symptoms, such as irritability, dysphoria or delusions.⁶

Clinicians play a key role in the medical management of AD, and provide recommendations and advice to patients and families/caregivers on a broad range of issues, including psychosocial problems, and legal and financial resources.⁷ Specialists involved in AD diagnosis

and management include neurologists, geriatricians and geriatric psychiatrists.

Therapeutic nihilism (disbelief in the efficacy or clinical value of a therapy) is a key issue in dementia management, particularly among clinicians, due to negative associations and stigma associated with this progressive illness.⁸ These perceptions should be overcome as they may delay diagnosis, referral, and treatment.⁸

This review provides recommendations on managing AD based on current knowledge and available pharmacologic agents. Support for patients, families, and caregivers is also discussed, from early recognition to difficult decisions around end-stage care. The goal of this approach is to maximize quality of life throughout the course of this complex disease. Data sources include pivotal clinical studies of donepezil, galantamine, rivastigmine, memantine, and medical foods identified using PubMed in 2014 and the relevant United States prescribing information. English-language articles considered of relevance to primary care physicians in relation to AD, its diagnosis and management, are included. Previous guidelines and management recommendations were reviewed. The recent meta-analysis of brain health activities by Alzheimer's Disease International was a key document.⁹

General Brain Health and Wellness

Modifying risk factors for cognitive dysfunction

There are potential risk factors for, or protective factors against, cognitive dysfunction. It is reasonable to recommend modifying these, based on the available evidence. Recommendations for maintaining brain health in adults with and without AD are summarized in Box 1.

Observational studies point to a protective role for certain nutrients and dietary patterns (Mediterranean diet). However, data from randomized controlled trials have been inconsistent. Whether factors such as cooking processes and other dietary components explain these inconsistencies is uncertain. The potential mechanisms by which certain nutrients may protect brain health also remain to be established.¹⁰

Long-term studies on the relationship between physical activity and the incidence of noncommunicable diseases in general is limited. However, the few available studies indicate that physical activity in healthy people is an important factor preventing the development of cognitive impairment and AD.¹¹

Depression is associated with cognitive decline,¹² supporting the management of depressive symptoms in the elderly. Further, there is clinical rationale to actively manage hyperlipidemia and diabetes.¹³ Untreated

Box 1. Recommendations for maintaining brain health in elderly patients with and without AD

- Consider following a Mediterranean-style diet, with fish, vegetables, legumes, fruit, cereals, unsaturated fatty acids (e.g., olive oil), and a limited amount of meat or dairy products.
- Consider taking supplements containing omega-3 (particularly docosahexaenoic acid), B-complex vitamins (including B12, B6, folic acid), and vitamin E.
- Keep alcohol intake to a low-to-moderate level (e.g., one glass of wine per day with dinner).
- Engage in regular physical activity.
- Maintain leisure and social activities – keep socially engaged.
- Continue or take up activities that help to stimulate the brain, e.g., Tai Chi, dancing, puzzles.
- Become educated about AD and seek support from others with AD, e.g., the Alzheimer's Association, Alzheimer's Foundation of America, Keep Memory Alive, and other community groups.
- Include music in daily life – listening to music, playing an instrument, singing.
- Maintain regular sleep patterns.
- Manage stress – stop doing things if they are becoming too stressful (e.g., volunteer work, answering the telephone), keep to a regular daily schedule, include relaxing activities (e.g., playing with pets, massage, and aromatherapy).

hypertension is associated with rapid decline in cognitive function in vulnerable individuals.¹⁴

A family history of AD is a risk factor for the disorder; family members should be encouraged to adopt a brain-healthy lifestyle.

Lifestyle considerations for patients with AD

Despite evidence that omega-3 fatty acids slow cognitive decline in the elderly, findings in patients with AD are inconsistent.^{15–17} One trial reported benefits of omega-3 fatty acid and lipoic acid treatment on cognition and ADL performance.¹⁶ However, due to small sample sizes, further studies are required.¹⁶ Folic acid and vitamin B supplements may help to preserve brain function.¹⁸ A small, double-blind, randomized, controlled trial reported that folic acid supplementation may improve response to cholinesterase inhibitor (ChEI) therapy.¹⁹ Time to institutionalization and daily living functioning have improved following vitamin E supplementation.^{20,21} As with all interventions, the benefit–risk ratio of supplements should be considered. A recent meta-analysis concluded that high blood levels of docosahexaenoic acid and eicosapentaenoic acid are possibly associated with increased risks of high-grade prostate cancer.²² These findings should be interpreted with caution due to the multifactorial etiology of prostate cancer, and the complex metabolism of long-chain omega-3 fatty acids.²²

Dementia symptoms are stressful for patients, caregivers, and families.^{23–26} Patients who believe nothing can be done about their illness are more likely to experience depression,²⁷ and clinicians should educate patients about steps they can take to preserve function (Box 1). Learning about AD and seeking support early in the disease course can help reduce stress and improve coping and health-related behaviors.²⁸ Artistic pursuits may help maintain a sense of identity and self-expression, improve aspects of behavior, and enhance communication.^{29–31} Music therapy reportedly improves language functions in patients with dementia³² and symptoms of anxiety and depression in patients with mild-to-moderate AD.³³ Interactions with pets may reduce agitation and anxiety in some patients with dementia.³⁴ Patients and caregivers can also reduce stress by adjusting activities to suit the patient's abilities, and keeping to a regular daily routine that includes relaxing activities.³⁵

Clinicians should urge patients with AD to participate in leisure activities, where possible, preserving function and quality of life.^{23,25,36} Cognitive training may improve function, so patients should be encouraged to learn new skills or hobbies and undertake activities that stimulate mental activity.^{12,37} Social interactions may be difficult for patients with AD, and they may withdraw due to self-consciousness, depression, or apathy.^{23,25} Participation in specialized adult day programs for patients with dementia may enhance the benefits of drug therapy and improve sleep quality, by keeping the patient engaged and reducing inactivity.³⁸ Specialized memory rehabilitation programs for patients with AD have also proven valuable,³⁹ but are not widely available.

Diagnosis

In clinical trials, the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) criteria are commonly used to diagnose dementia of the Alzheimer's type.⁴⁰ Recently, an updated version, DSM-5, was published; key updates are the change in dementia to the newly named entity "major neurocognitive disorder (NCD)", and recognition of a less severe level of cognitive impairment, termed "mild NCD".⁴¹

The most recent diagnostic guidelines from the National Institute on Aging and Alzheimer's Association define three stages of AD:⁴²

- Preclinical phase: neuropathologic changes occur, no overt (or only subtle) symptoms.
- Phase of mild cognitive impairment: symptoms become apparent; ADL are preserved; the patient does not have dementia.
- Dementia phase: ADL are impaired.

There may be preclinical neurologic changes in the form of cerebrospinal fluid or amyloid imaging biomarkers.⁴³ However, AD diagnosis is principally based on clinical criteria (Fig. 1);^{44,45} biomarkers can be used to define AD as the probable underlying cause of cognitive impairment, but are not strictly necessary for diagnosis.^{42,45} The accuracy of diagnosis is enhanced by integration of biomarkers. Table 1 outlines the recommended diagnostic steps.⁴⁶

Pharmacotherapy

There are a number of Food and Drug Administration (FDA)-approved pharmacotherapies for AD (Table 2). These may improve symptoms or delay decline; none impact the underlying neurodegenerative process.⁴⁷ It is important for patients and their caregivers to understand this, so they can make informed treatment decisions and have realistic expectations regarding the impact of treatment.⁴⁸

ChEIs

Three ChEIs (donepezil [Aricept[®]; Eisai Inc., Woodcliff Lake, New Jersey], galantamine [Razadyne[®]; Janssen Pharmaceuticals Inc, Titusville, New Jersey] and rivastigmine [Exelon[®] capsules and Exelon[®] Patch; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey]) are indicated for mild-to-moderate AD in the United States; donepezil and rivastigmine transdermal patch are also indicated for severe AD.^{49–52} All three ChEIs are approved in oral formulations;^{49–51} rivastigmine is the only ChEI also approved for delivery via a transdermal patch.⁵² Approval of high-dose 23 mg/day donepezil for moderate-to-severe AD was based on a randomized clinical trial that demonstrated greater cognitive efficacy versus the standard dose (10 mg/day).⁵³ The high-dose (13.3 mg/24 h) rivastigmine patch was approved for mild-to-moderate and severe AD, based on positive findings in the OPTIMA (OPTimising Transdermal Exelon In Mild-to-moderate Alzheimer's disease) and ACTION (ACTivities of daily living and cognitIOn) studies, respectively.^{54,55}

All three ChEIs have demonstrated clinical benefits on cognitive function, global clinical status,^{54–57} and performance of ADL.^{54–56,58} There are no proven clinically meaningful differences between the agents in terms of efficacy.^{56,57,59} Efficacy and tolerability associated with ChEIs are dose dependent,⁶⁰ so while high doses may be efficacious, adverse events (AEs) can be dose limiting. The agents have similar tolerability profiles, with nausea, vomiting, and diarrhea being the most common AEs.⁵⁶

Gastrointestinal (GI) AEs typically arise due to peaks in plasma drug concentrations.⁶¹ Strategies that reduce the

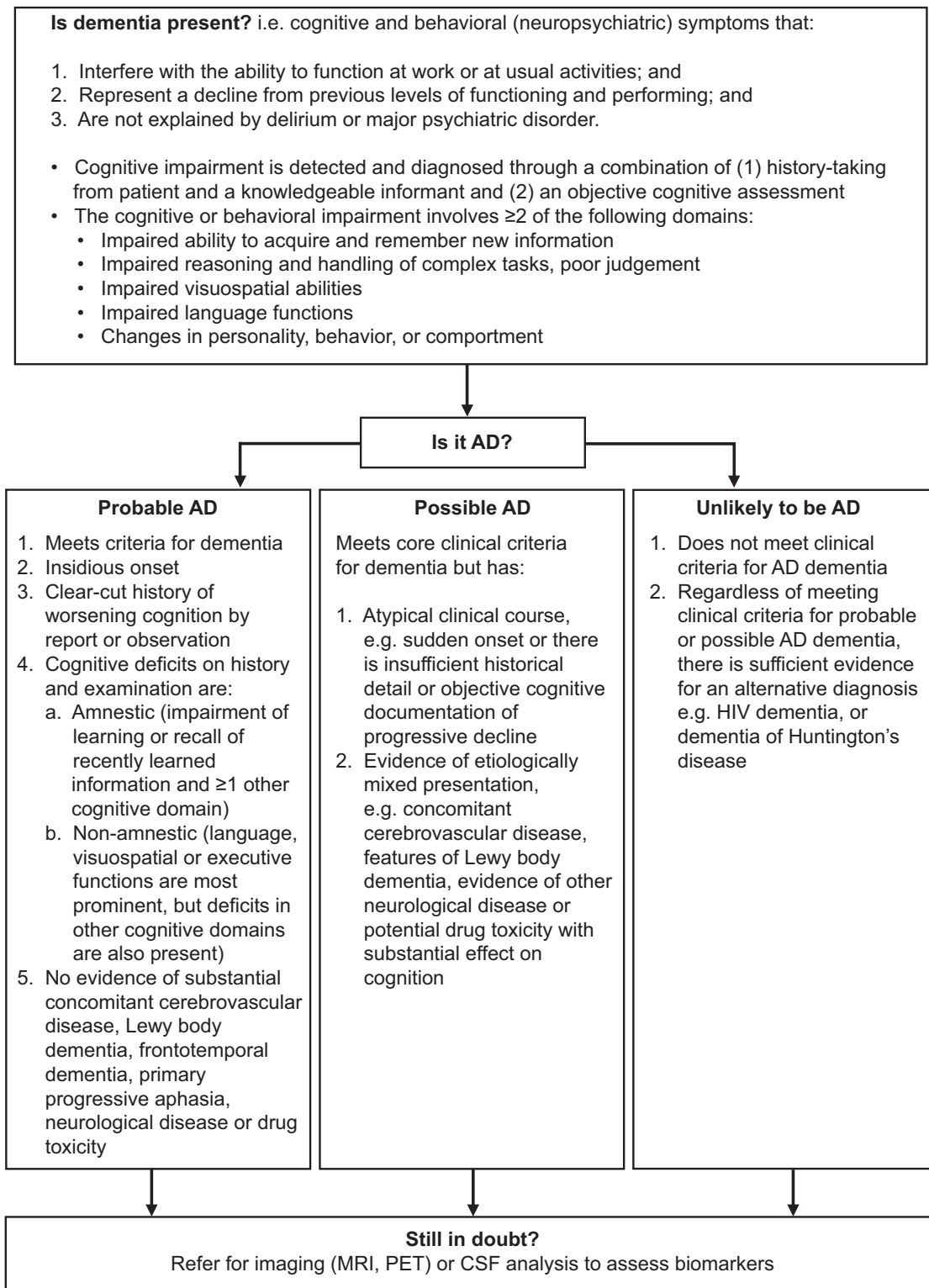


Figure 1. Diagnostic criteria for AD.⁴⁵ Permission to reproduce text used in this figure was kindly provided by Elsevier Limited. AD, Alzheimer's disease; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography.

Table 1. Steps in the diagnosis and assessment of a patient with suspected AD in primary care.⁴⁶

Step	Purpose	Tools/information required
Step 1: Prediagnostic tests	Identify risks for neurocognitive disorders	<ul style="list-style-type: none"> • Risk factor assessment • Medical history • Laboratory tests to identify risk factors and define comorbidities and early warning signs of preclinical dementia
Step 2: Assess performance	Cognitive assessment	<ul style="list-style-type: none"> • Cognitive tests e.g., MMSE,¹²⁶ Mini-cog,¹²⁷ MoCA,¹²⁸ SIB-8¹²⁹ • Informant-rated tools e.g., AD8¹³⁰
Step 3: Assess daily functioning	Determine level of independence and degree of disability	<ul style="list-style-type: none"> • Daily function assessment tool e.g., ADCS-ADL¹³¹
Step 4: Assess behavioral symptoms	Determine presence and degree of behavioral symptoms	<ul style="list-style-type: none"> • Behavioral assessment tool e.g., NPI-Q¹³² • Assess for other potential causes of behaviors (e.g., drug toxicity, medical or psychiatric comorbidity)
Step 5: Identify caregiver and assess needs	Identify primary caregiver and assess adequacy of family and other support systems	<ul style="list-style-type: none"> • Identify caregiver(s) and establish collaboration • Assess health of primary caregiver • Refer to psychologist, social worker, or other healthcare resources as needed
Other considerations	Identify cultural differences, language, and literacy level of patient and caregiver	<ul style="list-style-type: none"> • Recognize differences in illness interpretations and caregiving patterns between cultures • Be aware of preferred language • Recognize that paper-and-pencil tests and forms may not work well if patient or caregiver has literacy/language barriers

AD, Alzheimer's disease; AD8, 8-item Ascertain Dementia tool; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living scale; Mini-cog, Mini Cognitive Assessment Instrument; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NPI-Q, Neuropsychiatric Inventory Questionnaire; SIB-8, Severe Impairment Battery (8-item).

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dosing frequency, lower peak plasma concentrations, and reduce the rate at which peak concentrations are reached may improve tolerability.⁶² A sustained-release formulation of donepezil was developed to provide access to high therapeutic doses, while avoiding the rapid rises in peak drug plasma concentrations.⁵³ Donepezil 23 mg/day is associated with greater cognitive benefits in moderate-to-severe AD than donepezil 10 mg/day IR; however, there is an dose-related increase in AEs.⁵³

A pharmacokinetic analysis predicted lower peaks in plasma drug concentrations, but a similar area under the curve, with extended-release (ER) galantamine compared with the IR formulation.⁶³ During a clinical study, both once-daily galantamine ER and twice-daily galantamine IR (flexible dosing of 16 or 24 mg/day) demonstrated superiority to placebo on cognition in patients with mild-to-moderate AD, with a similar incidence of AEs observed in all three groups.⁶⁴

By providing sustained delivery over a 24-h period, transdermal delivery may improve GI tolerability and permit easier access to high-dose efficacy compared with oral dosing.⁶² Relative to 6 mg twice-daily oral rivastigmine, 9.5 mg/24 h rivastigmine transdermal patch was associ-

ated with comparable efficacy and two-thirds fewer GI AEs.⁶⁵ Rivastigmine patch treatment is initiated with the 4.6 mg/24 h dose, with up-titration to the minimum effective dose of 9.5 mg/24 h patch after at least 4 weeks, assuming good tolerability.⁵² After an additional 4 weeks, if well-tolerated, the dose may be increased to 13.3 mg/24 h patch.⁵² Continued use of the 4.6 mg/24 h dose can be considered in patients weighing less than 50 kg with tolerability concerns, or patients with mild-to-moderate hepatic impairment.⁵²

Transdermal delivery may be associated with application site reactions in some patients; the occurrence can be minimized by following the recommendations in the rivastigmine patch United States prescribing information.⁵² These include: rotating the application site; applying the patch only to clean, dry, hairless skin that is free of redness, irritation, cuts, or burns; and ensuring the skin is free of creams, lotions, or powders prior to patch application.⁵²

After initiating ChEI treatment, patients should be assessed after 2–4 weeks for the development of AEs,⁷ and after 3–6 months for effects on cognitive function and other behaviors/abilities.⁷ ChEI doses should be

up-titrated according to the prescribing information (Table 2).^{49–52} Regular follow-up appointments should be established to assess disease progression. Patients should be switched to another ChEI if they develop intolerable or nontransient AEs, if they do not respond to the initial agent (i.e., continued deterioration at pretreatment rate),⁷ or if caregiver or patient preferences change. The principle of switching is to transition the patient from one ChEI to another in an attempt to improve clinical outcomes. Switching should follow the recommendations outlined in the relevant prescribing information.^{49–52}

NMDA receptor antagonist

Memantine (Namenda[®]; Forest Pharmaceuticals Inc., St Louis, Missouri) is an *N*-methyl-D-aspartate (NMDA) receptor antagonist indicated for moderate-to-severe AD (Table 2).^{66,67} Clinical studies have demonstrated efficacy of memantine (20 mg/day) versus placebo on cognition, global function, and ADL performance.^{68,69} A high-dose (28 mg/day) once-daily ER formulation has demonstrated cognitive efficacy, and an acceptable tolerability profile, compared with placebo in patients with moderate-to-severe AD receiving ChEIs.⁷⁰ Memantine can be used as monotherapy⁷¹ or in combination with a ChEI.^{7,47} Combining two agents with different mechanisms of action, may improve efficacy relative to single-agent therapy, and the use of memantine with oral ChEIs may ameliorate ChEI-related GI AEs.⁴⁷

Medical foods

Several medical foods are available in the United States for management of AD and/or cognitive impairment, including:

- Caprylidene (Axona[®]; Accera Inc., Broomfield, California), a proprietary formulation of medium-chain triglycerides, intended for dietary management of mild-to-moderate AD.⁷²
- Cerefolin NAC[®] (PAMLAB, LLC, Covington, Louisiana), a combination of folic acid, vitamin B12, and *N*-acetylcysteine, intended for dietary management of mild cognitive impairment.⁷³
- Vayacog[®] (VAYA Pharma Inc., Greenville, South Carolina), a combination of phosphatidylserine, docosahexaenoic acid, and eicosapentaenoic acid, intended for dietary management of lipid imbalances associated with early memory impairment.⁷⁴

Noncarriers of the apolipoprotein ϵ 4 allele have shown significant improvements in cognitive function with caprylidene.⁷⁵ Currently, there is limited published evidence to support using folic acid, vitamin B12, and *N*-acetylcys-

teine,⁷⁶ except in the setting of hyperhomocysteinemia. However, in older adults receiving folic acid supplementation for 3 years, plasma homocysteine levels were reduced and memory function improved compared with placebo.⁷⁷

A 15-week, randomized, double-blind study reported that phosphatidylserine-containing omega-3 fatty acids improved cognitive performance in elderly with memory complaints without dementia, although further studies are required to confirm these findings.⁷⁸

Souvenaid[®] (Nutricia Advanced Medical Nutrition, Schiphol, The Netherlands) a combination of omega-3 fatty acids, uridine, choline, vitamins C, E, B6, and B12, selenium, and folic acid is not yet available in the United States. Souvenaid[®] is available in Europe (Food for Special Medical Purpose) as a dietary means of supporting synaptic integrity. In clinical trials of patients with mild AD, this combination demonstrated a significant improvement in delayed verbal memory,^{79,80} but not global cognition,⁷⁹ or performance of ADL.⁸¹

No single agent or combination will suit every patient, so clinicians should construct a comprehensive, integrated, multifaceted treatment plan that reflects the preferences of the patient and caregiver, and the most recent scientific guidance. Clinicians should be prepared to reassess their approach to achieve optimal therapeutic benefit/outcomes. The optimal duration of ChEI treatment has not been established, but patients in clinical trials have shown benefit for up to 4 years,⁸² so continuing treatment as long as patients tolerate the medication and families support treatment is reasonable. Maintaining open discussions with the family on disease progression and treatment outcomes may guide the clinician regarding whether or not to maintain treatment, and help the family to prepare for the eventual need for long-term residential placement.

Managing Comorbidities

In one study of 679 patients with AD in the United States, 61% had ≥ 3 medical comorbidities, and the number increased with advancing dementia severity.⁸³ After controlling for other variables, higher medical comorbidity was associated with worse cognitive function and poorer self-care.⁸³ Other data show that patients with AD are 55% more likely to be admitted to hospital than people without AD.⁸⁴ Common medical comorbidities in patients with AD include cardiovascular disease, thyroid dysfunction, sleep apnea, osteoporosis, glaucoma, cancer, falls, depression, infections, anorexia, rheumatoid conditions, and incontinence.^{85,86} One key treatable comorbidity is sleep apnea. In addition to being a risk factor for hypertension, stroke, and mortality,^{87,88} sleep apnea has

Table 2. (A) Food and Drug Administration-approved AD therapies and (B) medical foods.

	Mechanism	Approved/ intended indication	Administration		Frequency
			Route	Dosing	
(A) Pharmacologic agents					
Donepezil (Aricept [®]) ⁴⁹	ChEI	Mild-to-moderate AD • Moderate-to-severe AD	PO (tablet)	Titration: • Initiate 5 mg/day • May increase to 10 mg/day after 4–6 weeks • Severe AD: may increase to 23 mg/day after additional 3 months (minimum) Maintenance: • Mild-to-moderate AD: 5 or 10 mg/day • Moderate-to-severe AD: 10 or 23 mg/day	Once daily
Galantamine (Razadyne [®]) ⁵⁰	ChEI	Mild-to-moderate AD	PO (tablet/oral solution)	Titration : • Initiate: 8 mg/day • Increase to 16 mg/day after 4 weeks (minimum) • May increase to 24 mg/day after additional 4 weeks (minimum) Maintenance: • 16 or 24 mg/day	Twice daily, with food
Galantamine ER (Razadyne [®] ER) ⁵⁰	ChEI	Mild-to-moderate AD	PO (capsule)	Titration: • Initiate: 8 mg/day • Increase to 16 mg/day after 4 weeks (minimum) • May increase to 24 mg/day after additional 4 weeks (minimum) Maintenance: • 16 or 24 mg/day	Once daily, in morning, with food
Rivastigmine (Exelon [®]) ⁵¹	ChEI	Mild-to-moderate AD • Mild-to-moderate PDD	PO (capsules/oral solution)	Titration: • Initiate: 3 mg/day • If tolerated, may increase to 6 mg/day, and further to 9 and 12 mg/day after 2 weeks (minimum) at previous dose (4 weeks for PDD) Maintenance: • Mild-to-moderate AD: 6–12 mg/day • Mild-to-moderate PDD: 3–12 mg/day	Twice daily
Rivastigmine patch (Exelon [®] Patch) ⁵²	ChEI	Mild-to-moderate AD • Severe AD • Mild-to-moderate PDD	TD patch	Titration: • Initiate: 4.6 mg/24 h • After 4 weeks (minimum), if tolerated, increase to 9.5 mg/24 h • May increase to 13.3 mg/24 h after additional 4 weeks (minimum) Maintenance: • Mild-to-moderate AD: 9.5 or 13.3 mg/24 h • Severe AD: 13.3 mg/24 h	Apply new patch once every 24 h

(Continued)

Table 2. Continued.

	Mechanism	Approved/ intended indication	Administration		Frequency
			Route	Dosing	
Memantine (Namenda [®]) ⁶⁶	NMDA receptor antagonist	Moderate-to-severe AD	PO (tablet/oral solution)	<ul style="list-style-type: none"> Mild-to-moderate PDD: 9.5 or 13.3 mg/24 h Titration: <ul style="list-style-type: none"> • Initiate 5 mg/day • Increase to 10 mg/day, and further to 15 and 20 mg/day after 1 week (minimum) at previous dose Maintenance: <ul style="list-style-type: none"> • 20 mg/day 	Twice daily
Memantine (Namenda [®]) XR ⁶⁷	NMDA receptor antagonist	Moderate-to-severe AD	PO (capsules)	<ul style="list-style-type: none"> Titration: <ul style="list-style-type: none"> • Initiate: 7 mg/day • Increase dose (14, 21, and 28 mg/day) after 1 week (minimum) on previous dose Maintenance: <ul style="list-style-type: none"> • 28 mg/day 	Once daily
(B) Medical foods					
Caprylidene (Axona [®]) ⁷²	Medical food – nutritionally supports brain metabolism	Mild-to-moderate AD	PO (powder to be added to 4–8 oz of liquid)	<ul style="list-style-type: none"> Titration: <ul style="list-style-type: none"> • 8–10 g/day for 2 days • Increase dose by 8–10 g every other day, as tolerated, up to a maximum of 40 g/day Maintenance: <ul style="list-style-type: none"> • 40 g/day 	Once daily after food
L-methylfolate/methylcobalamin/ <i>N</i> -acetylcysteine (CerefolinNAC [®] , Triveen-CF NAC [®]) ⁷³	Medical food – supports the brain's metabolic balance	Mild or moderate cognitive impairment	PO (caplet)	1 caplet/day	Once daily
Phosphatidylserine/docosahexaenoic acid/eicosapentaenoic acid (Vayacog [®])	Medical food – supports management of lipid imbalances	Early memory impairment	PO (capsule)	1 capsule/day	Once daily
Omega-3 fatty acids, uridine, choline, vitamins C, E, B6, and B12, selenium, and folic acid (Souvenaid [®])	Medical food – supports synaptic integrity	Early AD	PO (liquid)	1 bottle (125 mL) per day	Once daily

In contrast to FDA-approved drugs, no premarket review process exists for medical foods: data supporting their effectiveness (if such data exist) have not undergone the same rigorous scientific scrutiny as approved drugs. AD, Alzheimer's disease; ChEI, cholinesterase inhibitor; ER, extended release; NMDA, *N*-methyl-D-aspartate; PDD, Parkinson's disease dementia; PO, per os (oral administration); TD, transdermal.

been reported as a significant risk for dementia in older women, nearly doubling the risk for mild cognitive impairment and dementia over 5 years.⁸⁹ It is therefore important for clinicians to evaluate the presence of sleep disordered breathing as another modifiable risk.

It is important for clinicians to manage conditions comorbid to AD (Box 2). This can limit cognitive and functional decline,⁸⁵ and reduce the risk of hospital admission, which can be disorienting, distressing, and lead to medication discontinuation. Moreover, medical

illness and pain are common triggers for agitation or aggression in patients with AD,⁴⁷ so early recognition and treatment of comorbid medical conditions can limit neuropsychiatric and behavioral symptoms.

Neuropsychiatric symptoms are a key component of AD, affecting almost all patients over the disease course.⁹⁰ Studies suggest that more than 90% of patients with AD show behavioral or neuropsychiatric symptoms, including depression, agitation, anxiety, psychosis, hallucinations, apathy, eating disorders, disinhibition, and sleep distur-

bances.^{91–93} The first step in management is to rule out potential medical and/or somatic causes, for example, lower urinary tract infection,^{7,86,94} and recommend non-pharmacologic interventions (Table 3).⁷ ChEIs or memantine may delay or relieve symptoms,^{7,86,95} but some patients may require targeted pharmacotherapy, such as antipsychotics or antidepressants. Although antidepressant agents may be efficacious in treating depression in patients with AD, the supporting evidence is limited, and no agent has been approved specifically for depression or psychosis of AD.^{96,97} A cross-sectional study reported that treatment of neuropsychiatric symptoms in elderly patients with dementia residing in care homes is generally not syndrome specific, and included use of neuroleptics and other substances not indicated for dementia.⁹⁸ Anti-psychotic use has been associated with an increased risk of death due to pneumonia in elderly patients with dementia,⁹⁴ highlighting the importance of investigating the underlying cause of behavioral symptoms prior to prescribing treatment.

Patients with AD exhibiting agitation and other neuropsychiatric symptoms often receive anticonvulsants, such as divalproex, as a second-line treatment.^{99,100} However, data from controlled clinical studies suggest divalproex accelerated brain atrophy, and did not benefit patients with moderate AD in terms of neuropsychiatric symptoms, functional abilities, and cognition.^{101,102}

There is significant potential for polypharmacy in patients with AD.¹⁰³ Clinicians should be aware of potential drug interactions when introducing new medications and of difficulties in maintaining compliance/adherence with complex drug regimens.¹⁰³ Attempts should be made to simplify the medication regimen, for example, use of alternate modes of delivery that are more user friendly.¹⁰³

Box 2. Management of comorbidities

- Assess regularly for medical and neuropsychiatric comorbidities.
- Manage comorbidities, particularly cardiovascular risk factors, with lifestyle recommendations and medications to reduce risk of cognitive decline.
- Investigate potential medical, somatic, or medication-related reasons for any new change in function or behaviors.
- Promptly treat acute medical illnesses to reduce the risk of hospital admission.
- Offer caregiver education and support to help manage neuropsychiatric or behavioral symptoms (Table 3).
- Initiate psychoactive medication as necessary, balancing the benefits and risks, and document a discussion with the patient and/or family members in the medical record.
- Be aware of adverse impact of polypharmacy and potential for drug–drug interactions.
- Encourage adherence – simplify medication regimen, where possible.

Table 3. Nonpharmacologic approaches to manage common behavioral symptoms and mood disorders.⁷

Behavioral symptom	Nonpharmacologic intervention
Apathy	Stimulation/activities <ul style="list-style-type: none"> • Simple tasks
Sleep disturbances	Take steps to maintain regular, good quality sleep <ul style="list-style-type: none"> • Stimulation during the day (especially adult day services) • Reduction in excessive stimulation/noise in the evening
Irritability/agitation	Break down tasks into simple steps <ul style="list-style-type: none"> • Redirection
Wandering	Visual cues <ul style="list-style-type: none"> • Exercise • Safe places to wander • Enrollment in wandering assistance schemes
Mood disorders	Exercise
Psychotic disorders	Reassurance <ul style="list-style-type: none"> • Distraction rather than confrontation • Removal of potential sources of confusion, e.g., mirrors
Eating/appetite disorders	Offering simple, finger foods <ul style="list-style-type: none"> • Removal of distractions from dining area • Soothing music

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Societal and Financial Impact

Residential care is a major contributor to the financial impact of AD. In several studies ChEI treatment was associated with a delay in time to nursing home placement,¹⁰⁴ an effect that is reportedly dose dependent.¹⁰⁵ Similarly, evidence suggests cost-savings with memantine compared with nonpharmacological treatment in moderately severe-to-severe AD,¹⁰⁶ as well as some benefit for combined ChEI/memantine therapy based on health-care data from France.¹⁰⁷

Nonpharmaceutical interventions in the management of behavioral symptoms and mood disorders have also been linked to improved cognitive and functional ability, enhanced patient and caregiver quality of life and delayed institutionalization.⁷

Other Considerations

Clinicians responsible for patients with AD should pay attention to several areas that may impact well-being, and not only medication (Box 3).

Safety

Keeping the person with AD safe is important, to prevent injuries, maximize function, minimize stress and agitation, and reduce caregiver burden.⁷ A home assessment may be useful to identify hazards that could increase the risk of falls. Patients with AD may no longer remember how to use appliances correctly, identify toxic substances, or handle sharp objects, so caregivers should ensure that potentially harmful objects are removed.⁷ The Alzheimer's Association, Alzheimer Foundation of America, and other advocacy groups have resources on how to assess and manage patient safety in the home.¹⁰⁸

Approximately 60% of US households that have a family member with dementia have a gun.¹⁰⁹ Few laws regulate gun ownership in relation to age or cognitive function.¹¹⁰ Since patients with dementia may develop aggressive behaviors toward themselves and others as the disease progresses,¹¹¹ firearms pose a risk of serious injury.¹¹⁰ When it comes to gun ownership, clinicians need to balance the patient's right to autonomy against the need for safety.^{7,112}

Patients with AD will have to stop driving when their limitations make it unsafe. Discussing this possibility early in the disease course can help planning.¹¹³ Clinicians should be familiar with their state's regulations regarding minimum cognitive requirements for licensure, and legal requirements for reporting the diagnosis. The American Occupational Therapy Association website (<http://www.aota.org>) identifies resources for people with AD and their families, including a national database of driving specialists, who can evaluate and offer strategies to reduce driving risk.

Ongoing follow-up

Clinicians need to regularly assess the patient for changes in daily functioning, cognitive status, comorbidities, behavioral symptoms, medication requirements, and care needs; any sudden changes require attention.⁷ Weight loss occurs in ~40% of patients with AD.¹¹⁴ Patients showing signs of weight loss should be offered nutritional supplementation and advice on increasing daily calorie intake. Dosing modifications may also be appropriate for these patients.

Abuse

Clinicians are well placed to identify potential patient abuse and neglect, or signs of overwhelming stress and abuse in caregivers.⁷ It is important to recognize that abuse may be exerted by the patient on the caregiver or vice versa.⁷ Effective management of aggressive symptoms or psychiatric comorbidities is essential, as is timely referral to support services. Across the United States, a number of elder abuse multidisciplinary teams exist,

Box 3. Checklist for clinicians caring for patients with AD

Health

- Have you provided the patient/caregiver with nutritional advice?¹²⁰
- If using a transdermal patch, have you provided the patient/caregiver with guidance on best patch use, including skin care?⁵²
- Are you regularly assessing your patient's clinical and functional state?

Safety

- Have you or has someone else (caregiver, social worker) assessed the safety of the patient's home?¹¹³
- Have you asked your patient and their caregiver(s) about firearms in the home?¹¹³
- Have you talked to your patient and their caregiver(s) about the likely need to stop driving?¹²¹

Legal considerations

- Have you advised your patient and their caregiver(s) to seek legal advice with regard to planning for future incapacity?¹²²
- Are you aware of the state requirements regarding medical fitness to drive for patients with AD?¹²¹
- Are you aware of your legal obligations/appropriate steps to take if you suspect abuse/neglect in the patient or caregiver?¹²³

Support

- Are you regularly assessing how the caregiver is coping and the caregiver's physical health?¹²⁴
- Have you provided the caregiver with information on how to access local support services?¹²⁵

which provide expert consultation to service providers, and identify service gaps and systems problems when managing cases of abuse.¹¹⁵

Residential care and legal aspects

The most common reasons for patients to move to residential care are the need for more skilled care than the caregiver can provide, the caregiver's health, and the patient's dementia-related behaviors.¹¹⁶ Discussing the potential future need for residential care early in the disease course, and identifying the threshold for such decisions, can ease the process. Clinicians should advise patients and their caregivers to plan for when the patient will have diminished capacity, and seek legal advice to put in place the necessary powers of attorney, as well as documentation around end-of-life preferences, such as wills and advance directives/living wills.⁷

Caregiver well-being

The importance of shaping policy and practice to support the caregiver cannot be overemphasized.¹¹⁷ Demands on

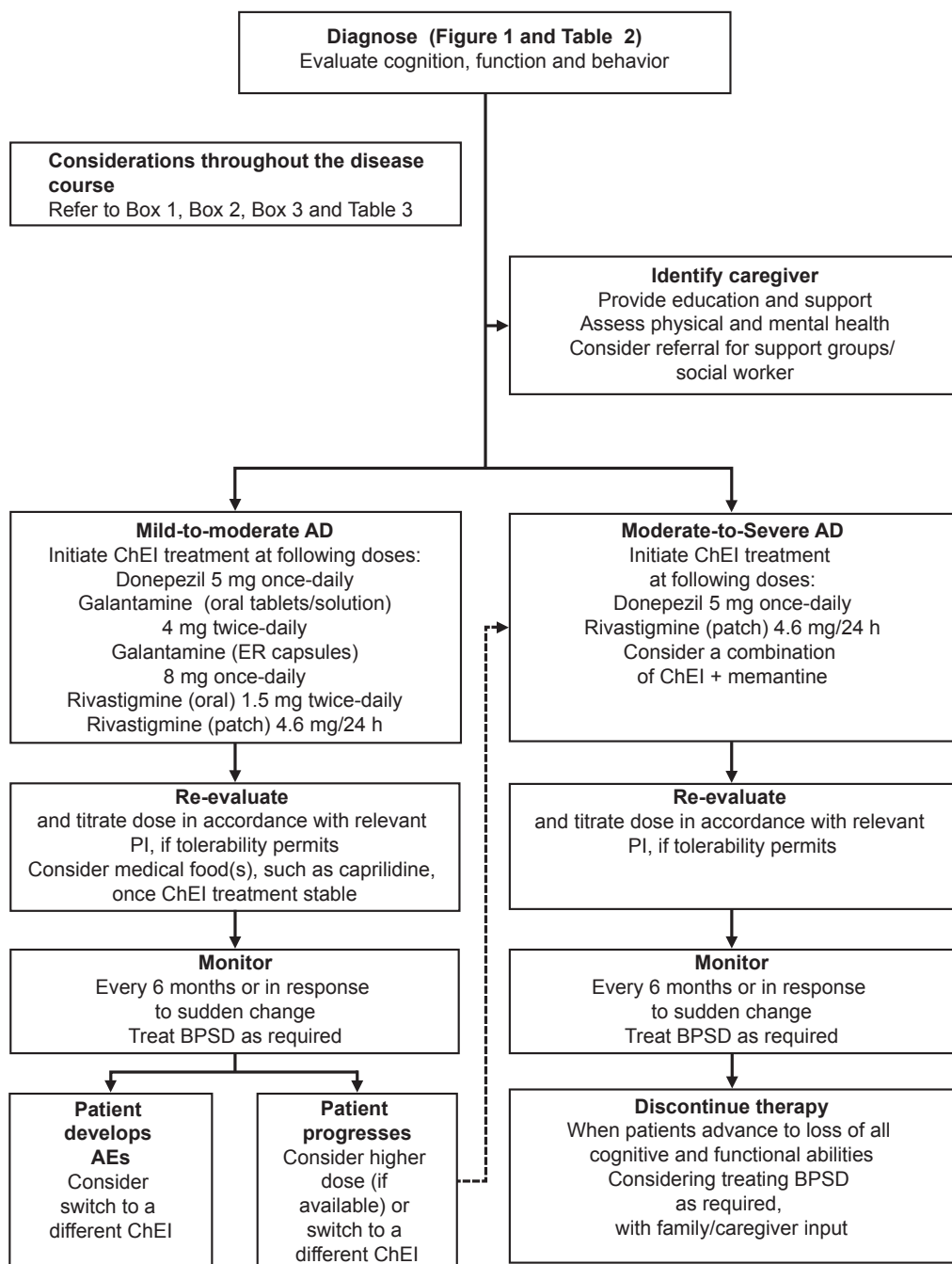


Figure 2. Treatment and management of AD.⁴⁷ Permission to reproduce this figure was kindly granted by *Physician's Weekly*. AD, Alzheimer's disease; BPSD, behavioral and psychological symptoms of dementia; ChEI, cholinesterase inhibitor; ER, extended release; PI, prescribing information.

caregivers increase as the disease progresses, and may include managing bathing, dressing, feeding, and toileting.⁸⁶ Caregivers must cope with sometimes challenging behaviors while dealing with the emotional impact of the changes to their relationship with the patient. They are essential in providing information to healthcare profes-

sionals about symptomatic and functional changes in the patient.¹¹⁸ Clinicians should pay careful attention to the physical and psychological health of caregivers.¹¹⁹ Education, support, counseling, respite care, and referral to other services may be required. Involving a social worker early in the course of the disease can help caregivers gain

access to local support services and provide advice around financial assistance.⁷

Summary

AD is one of the most challenging chronic conditions to manage. Treatment must be individualized for the symptoms, functional status, comorbidities, behaviors, and the psychosocial situation of each patient, and requires regular reassessments for changes in the patient's and caregiver's medical, mental, and psychological states. Figure 2 shows an algorithm for how to manage AD in primary care. Early diagnosis, referral to specialists, and treatment initiation are key; as are understanding and conveying realistic expectations of treatment. Patients respond individually to different interventions, so clinicians should be willing to change medications to maximize patient and caregiver quality of life, and to engage the assistance of other healthcare professionals (e.g., geriatricians, neurologists, psychiatrists, psychologists, physical or occupational therapists, social workers). It should be emphasized to patients and caregivers that, while the progressive course of AD cannot be reversed, lifestyle changes and medication can delay the progression of cognitive and functional symptoms of AD and maximize quality of life.

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Conflicts of Interest

Jeffrey L. Cummings has provided consultation to Acadia, ADAMAS, Anavex, Avanir, Avid, Baxter, Bristol-Myers Squibb, Eisai, Elan, EnVivo, GE, Genentech, Lilly, Lundbeck, MedAvante, Merck, Neuronix, Novartis, Otsuka, Pain Therapeutics, Pfizer, Prana, QR, Sanofi, Takeda, Toyama and UBC. Jeffrey L. Cummings owns stock in ADAMAS, Prana, Sonexa, MedAvante, Neurotrax, Neurokos, and QR pharma. Jeffrey L. Cummings has participated as a speaker/lecturer for Eisai, Forest, Janssen, Novartis, Pfizer, and Lundbeck. Jeffrey L. Cummings owns the copyright of the Neuropsychiatric Inventory. Jeffrey L. Cummings has provided expert witness consultation regarding olanzapine and ropinirole. Richard Isaacson has served as a scientific advisor/consultant for Novartis and Accera in the last year. Frederick A. Schmitt has received research funding in the past from Pfizer and Forest Laboratories, and presently serves on a data safety

monitoring committee for Pfizer. Drew Velting is an employee and stock holder of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey.

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