Effective Pharmacological Management of Alzheimer's Disease

Alireza Atri, MD, PhD

Abstract

Alzheimer's dementia represents organ failure of the brain. It denotes a clinical milestone that is the result of a pathological process, Alzheimer's disease (AD), which over 1 or more decades has wrought insidious destruction, and finally overwhelmed the brain's capacities to compensate. It is incurable, progressive, and follows an individual pace and course. AD is particularly demanding and devastating to family and caregivers, and patients, all of whom suffer psychologically and emotionally.

The cholinesterase inhibitors (ChEIs) donepezil, galantamine, and rivastigmine and the N-methyl-D-aspartate receptor antagonist memantine are approved by the US Food and Drug Administration for AD; they are often used in combination once the disease reaches moderate stages. The relatively good safety profile of these medications, along with their efficacy in alleviating symptoms, is supported by several level-I evidence-grade, short-term, randomized, placebo-controlled trials (RCTs). However, these studies are of limited value in assessing the real-world clinical and economic impact of AD therapies. Long-term, observational studies can provide complementary information to results from short-term clinical trials and more accurately assess practical long-term benefits, risks, costs, and effects on clinically meaningful end points.

There is now accumulating and convergent evidence from short- and long-term RCTs, longer-term open-label extensions of RCTs, and long-term observational studies that ChEIs and memantine reduce decline in cognition and daily function, and delay nursing home placement. Optimal care in AD is multifactorial; it includes early diagnosis and multidisciplinary care with educational and nonpharmacological interventions, while ensuring safety, treating comorbidities, caring for caregivers, and appropriate initiation and maintenance of combination therapy.

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For author information and disclosures, see end of text.

The dementia stage of Alzheimer's disease (AD) reflects organ failure for cognitive, functional, and behavioral systems of the brain. It is a by-product of complex biochemical and neuropathologic processes a decade or more in the making that are incompletely understood and different from normal aging. The neurodegenerative hallmarks of AD include accumulation of soluble and toxic amyloid-beta-42 oligomers, destruction of synapses, dysregulation of coordinated intrinsic brain networks, deposition of amyloid plaques, formation of neurofibrillary tangles, dysfunction of multiple neurotransmitter systems (including glutamate, acetylcholine, and serotonin), neuronal loss, and inflammation.[1]

The insidiousness of AD in its mild stages partially reflects a lack of recognition of symptoms and underdiagnosis. Over time, however, distinguishable AD characteristics emerge that exceed the customary ignorable thresholds of "normal aging" and "senior moments," and finally raise suspicions for a disorder. While cognition and memory disruptions are important features in AD, perhaps the earliest and most troublesome symptoms are noncognitive behavioral (ie, neuropsychiatric) symptoms that often go unrecognized for years. Heightened anxiety and depressive symptoms—particularly apathy and withdrawal—are highly prevalent in preclinical and early stages of AD.[2] Progression to later-stage symptoms such as impaired judgment, disorientation, and confusion; major behavioral changes such as aggression and agitation; and neuropsychiatric symptoms such as delusions and hallucinations can go unrecognized until AD diagnosis.[3] Recognition of early warning signs is of paramount importance—optimal management relies on accurate and timely diagnosis.

AD affects the entire family. Family and caregivers of individuals with AD report severe stress. The optimal diagnosis and management of AD involves a close alliance with AD caregivers and requires early diagnosis, multimodal management, and multispecialty care.

AD exacts an immense and expanding financial burden on families and societies. The total costs of AD to society are often underestimated; much of the costs due to lost wages and productivity, and illness suffered by caregivers of patients with moderate to severe AD (who provide on average 400-500 hours of caregiving time) are not completely accounted for in these calculations.[4]

Initial pharmacologic management of AD consists of eliminating therapeutic redundancies and potentially deleterious medications (ie, according to Beers Criteria[5,6]). A pharmacologic foundation of combination therapy with a cholinesterase inhibitor (ChEI) and memantine reduces decline in cognition and function, delays the emergence and impact of neuropsychiatric symptoms, and works best when appropriately instituted early and maintained.

Table 1. Drugs Approved by the FDA for AD[10-15]

Drug	Indication	Date of Introduction
Tacrine	Mild to moderate dementia of the Alzheimer's type	1993
Donepezil	Dementia of the Alzheimer's type	1997
Rivastigmine (oral)	Mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease	2000
Rivastigmine patch	Mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease	2008
Galantamine	Mild to moderate Alzheimer's disease	2001
Memantine	Moderate to severe dementia of the Alzheimer's type in adult patients	2003

AD indicates Alzheimer's disease; FDA, US Food and Drug Administration.

The major practical issues associated with pharmacologic treatment of AD surround its rationale and the expectations of treatment; when to start and stop therapy, what to expect, and how to appraise the value of treatment are all crucial questions for patients, families, and prescribing physicians to discuss and understand. There is no cure for AD; the current AD treatment paradigm is one of management of symptoms and reduction of decline.

Short-term responses to AD medications vary greatly between individuals. During the initial 6 to 12 months of treatment, patients' performance on measures of cognition, activities of daily living, behavioral symptoms, and global clinical impression of change may significantly improve in a minority (10%-20%), plateau in nearly half (30%-50%), or continue to deteriorate in a third (20%-40%). Estimates for number needed to treat for stabilization or improvement in 1 or more clinical domains (eg, cognition, function, behavior, global severity) range from 5 to 9:1 for ChEI and memantine monotherapy and combination therapy in AD.[7,8] The rate of marked clinical worsening, defined by significant deterioration that is simultaneously observed in several clinical domains, was also reduced in half with combination therapy in moderate to severe AD.[9] With sustained pharmacological treatment, the care plan for any individual patient should be evidence-based and provide the modest expectation of overall stabilization in the short term and reduction of clinical decline in the long term. It is important for clinicians, patients, and families to understand that, in the long-run, current AD treatments mitigate but do not prevent decline.

Sustained AD management can provide long-term symptomatic benefits by attenuating, delaying, and shortening the duration of problematic behaviors that emerge as the disease progresses. In the very severe stages of AD, when patients with profound functional and behavioral disturbances require nearly constant attention and supervision, institutionalization may be necessary. It is generally in the late stages of AD that the greatest emotional and economic costs are exacted.

Pharmacologic Therapy for AD

Two classes of medications are approved by the US Food and Drug Administration (FDA) for AD: ChEIs (donepezil [Aricept], galantamine [Razadyne], and rivastigmine [Exelon]) and the N-methyl-D-aspartate (NMDA)-receptor antagonist memantine (Namenda) (Table 1).[10-15] These drug classes work on different but complementary neurochemical pathways; both are important in cortical information processing, and cognitive functions, especially memory, learning, attention, and arousal.

Tacrine was the first ChEI approved for clinical use, but it is no longer prescribed due to a relatively unfavorable administration schedule (4 times daily) and side-effect profile (potential hepatotoxicity).[10] Various preparations of ChEIs are available: oral (once and twice daily), orally disintegrating tablets, oral elixir, and once-daily patch. Generic galantamine and donepezil are available in the United States. There is no compelling evidence to support superior efficacy for any particular ChEI. Efficacy is generally dose related, but tolerability diminishes (particularly due to gastrointestinal [GI] side effects of cholinergic stimulation: flatulence, increased GI secretions, loose stools) at high dosages. Some procholinergic side effects of ChEIs can be ameliorated by coadministration with memantine. ChEI use is contraindi-

cated in patients with active peptic ulcer disease/GI bleeding, unstable cardiac arrhythmia or disease, uncontrolled epilepsy, and unexplained syncope. Pharmacokinetic half-life depends on the type of ChEI and formulation, but can range from 4 to 50 hours. ChEIs are hepatically cleared.[11-14]

Memantine is the only AD medication in its class (NMDA-receptor antagonists). It is available as oral tablets and in liquid formulations. Titrated appropriately, memantine has a highly favorable safety and tolerability profile. Mild and transient treatment-emergent side effects include confusion, dizziness, constipation, headache, and somnolence, and may be encountered during titration to the maximum total daily dose of 20 mg or soon after. Dose-adjustment to a 10-mg daily dose (5 mg twice daily) is recommended in patients with severe renal insufficiency (creatinine clearance <30 mL/min). Memantine has a pharmacokinetic half-life of 60 to 80 hours and is renally excreted.[15]

Many medications are used off-label by clinicians to manage symptoms associated with AD. This is usually to combat the noncognitive behavioral symptoms (NCBS) and problem behaviors in advancing AD. Most notable are the antipsychotics that carry a black box warning in the United States due to the increased relative risk (RR) of adverse cardiovascular outcomes, stroke, and death. They are associated with a 1.5 to 1.7 increase in RR with a 1% absolute increased risk of death in elderly demented patients.[16,17] Other side effects associated with antipsychotics include extrapyramidal symptoms/parkinsonism, somnolence, dystonia, gait disturbances, and cognitive impairment.[18,19] First-generation antipsychotics tend to have more side effects than second-generation antipsychotics. The negative effects of antipsychotics on cognition were supported in a meta-analysis where antipsychotics were associated with reductions in Mini-Mental State Exam (MMSE) scores comparable to the degree that ChEIs reduce declines in scores.[16]

While a variety of other medications, most notably antidepressants, are often prescribed in clinical practice to manage mood and anxiety symptoms and problem behaviors (eg, aberrant and repetitive motor activity) in AD, they are used in an off-label manner without high-grade evidence for their clinical efficacy in this population.

Clinical Trials in AD

Many randomized, double-blind, placebo-controlled trials (RCTs) have studied patients across the AD severity spectrum to assess the clinical efficacy of anti-AD medications. These RCTs provide level I evidence for 24- to 28-week treatment efficacy and safety in patients with AD. While the majority of these RCTs evaluated efficacy of ChEIs or memantine monotherapy,[20-25] several assessed efficacy of combination therapy consisting of a ChEI and memantine.[26,27]

Limitations of these "explanatory" RCTs include their performance under idealized conditions in highly selective samples, and short durations relative to the long course of illness in AD.

Primary and secondary efficacy measures in these explanatory RCTs consist of change from baseline in domain-specific functions (eg, cognition, activities of daily living, behavior, global function/severity). Measures to assess cognitive function have included the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), Severe Impairment Battery (SIB), and MMSE; a common measure for activities of daily living (ADL) function was the Alzheimer's Disease Cooperative Study (ADCS)-ADL score; and a frequent measure of noncognitive behavioral function was the Neuropsychiatric Inventory (NPI). Several different measures of global stage and severity (eg, Clinical Dementia Rating [CDR] scale) as well as overall clinical impression of change have also been utilized.

ChEIs administered as monotherapy have demonstrated efficacy in short-term RCTs in mild AD. The efficacy of memantine in mild AD, alone or in combination with a ChEI, has not been demonstrated by an RCT.[27] However, overall findings have otherwise been consistent across domains in these short-term RCTs: treatment with a ChEI, memantine, or their combination provides significant benefits over placebo in the moderate to severe stages of AD. Tariot et al performed the pivotal RCT that demonstrated the safety, tolerability, and efficacy of combination therapy in moderate to severe AD.[28] In this 24-week RCT, 403 patients (MMSE range 5-14 at baseline) already receiving stable doses of donepezil for approximately 2 years continued with donepezil treatment and were subsequently randomized to receive (after titration) memantine 10 mg twice daily or placebo. The combination was associated with significantly better scores for measures of cognition (SIB, P <.001), ADL (ADCS-ADL$_{19}$, P <.05), and behavior (NPI-total, P <.01) compared with placebo. Memantine and donepezil combination therapy was also associated with a significantly higher rate of study completion (P = .01) and fewer discontinuations due to adverse events (7.4% vs 12.4%).

Open-label follow-up studies of RCTs of various durations provide support for the cognitive benefits of ChEIs in patients who continue taking these medications; for donepezil, the benefit may be up to 2.8 years[29] to 4.9 years[30]; for rivastigmine it may be up to 2 years[31] to 5 years[32]; and for galantamine it may be up to 1.5 years[33] to 3 years.[34] Limitations of open-label extension studies of RCTs include potential confounds due to possible effects of differential attrition, unblinding, and

the absence of a control group for comparisons during the open-label phase.[35]

Meta-Analyses of AD Clinical Trial Data

Meta-analysis results are more reflective of heterogeneous populations and several support the benefits of ChEI and memantine therapy in AD. A meta-analysis by Jones et al that included 3403 patients with AD (MMSE scores between 10 and 26) from 13 RCTs of donepezil versus placebo conducted between 1990 and 1999 supported the benefits of donepezil treatment over the decade.[20] This provided further support to findings from the Cochrane Database meta-analyses of short-term RCTs that ChEIs significantly improve, stabilize, or reduce cognitive decline in AD (eg, in the short-term, ChEIs provided a mean improvement of 2.7 points over placebo on the 70-point ADAS-cog scale).[21] Other meta-analyses also support the benefits of ChEIs compared with placebo, and report small to medium standardized effect-size estimates of treatment.[36,37]

Meta-analysis of RCT data for memantine also supports its broad benefits in the treatment of AD. Winblad and colleagues' meta-analysis of 6 memantine RCTs in patients with moderate to severe AD (n = 1826) assessed measures of global status (Clinician's Interview-Based Impression of Change plus Caregiver Input), cognition (ADAS-cog subscale or SIB), daily function (ADCS-ADL 19- or 23-item scale), and behavior (NPI).[38] They reported significant superior efficacy for memantine versus placebo in all outcome domains, small to medium standardized effect-size estimates, good tolerability, and a favorable adverse event profile. Areosa et al reported that memantine was associated with significant benefits in cognition (P = .02 vs placebo) and behavior (P = .04) that were supported by congruent benefits in clinical global impression of change (P = .005) in mild to moderate AD. In moderate to severe AD, memantine was associated with significant beneficial effects in cognition (P <.00001 vs placebo), daily function (P = .002), and behavior (P = .002), which were also supported by similar benefits in clinical global impression of change (P = .002).[39]

Necessity of Long-Term Studies

AD is a disease with a long duration of illness that usually spans many years from diagnosis to death. Therefore, studies lasting less than 1 year are of limited value in regard to the real-world clinical and economic impact of AD therapies. In short-term RCTs (lasting 24 or 28 weeks), participants were selected based on strict screening criteria and enrolled subjects were subsequently closely monitored to adhere to tight study protocols. In some trials, patients with common comorbid conditions, such as severe agitation, or those taking antipsychotic medications were excluded, and those with variable adherence to treatment were withdrawn from studies. These procedures produce subject homogeneity. However, given the large heterogeneity of the AD clinical population, it cannot be assumed that positive outcomes will translate to similar benefits or will readily identify long-term treatment risks in the clinical setting.

Practical and ethical constraints limit the duration of RCTs in the clinical setting. Only a few industry or publicly sponsored trials have lasted longer than 1 year, and most are open-label extensions of short-term trials. A large, long-term RCT, however, is ongoing in the United Kingdom.[40]

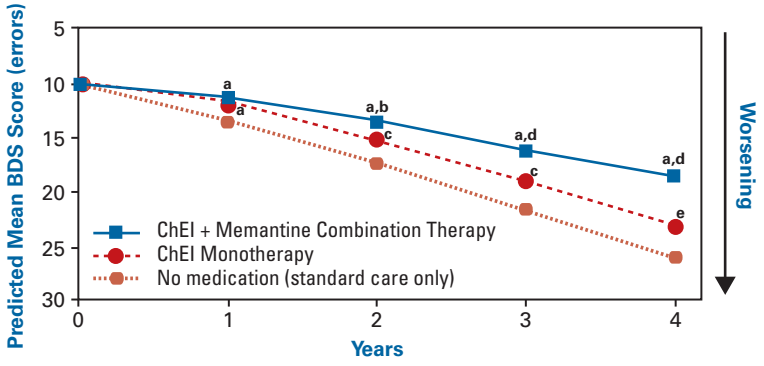
One randomized study originally scheduled for 60 weeks sought to introduce modifications in study design, enabling an extension to 4 years. The study faced several challenges; it recruited less than 20% of its targeted enrollment based on its power projections. Then, of the total of 565 community-based patients with mild to moderate AD that were randomized, just 4 of the 7 remaining eligible patients chose to enroll for a fourth year, demonstrating some of the practical difficulties in conducting such studies.[41]

Naturalistic, longitudinal studies reflect real-world outcomes in AD and dementia because they include patients with significant comorbidities who may be taking several medications and have imperfect adherence to treatment regimens. They include larger study populations, are of longer duration, assess measures other than those required for regulatory approval, and gather data on patients over multiple disease stages.

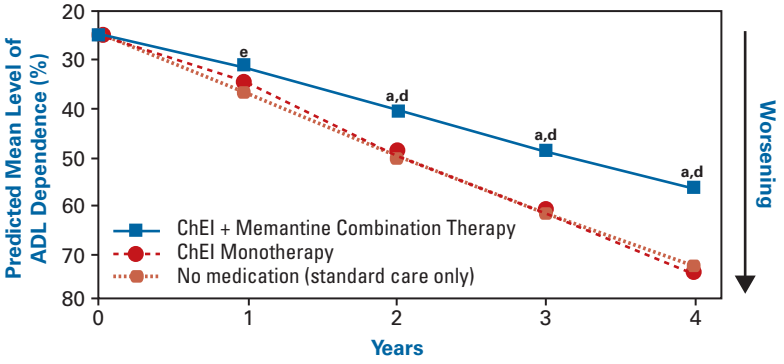
The real-world clinical effectiveness and long-term trajectory of cognitive and functional outcomes associated with AD medications were assessed in a naturalistic, observational cohort of patients enrolled in an academic memory unit and AD research center.[42] The study compared 3 treatment cohorts: ChEI plus memantine (combination therapy) (n = 116), ChEI alone (n = 122), and standard care without ChEI or memantine (n = 144). Cognition was assessed by the Information-Memory-Concentration subscale of the Blessed Dementia Scale (BDS) and daily function by the Weintraub ADL scale. Mean follow-up was 30 months. Mixed-effects regression analysis with adjustment for baseline covariates and group differences showed significant reductions in decline on BDS and ADL scores over time in the patient cohort receiving combination therapy compared with ChEIs alone (P <.001) and standard care without ChEI/memantine (P <.001) (**Figure**). Standardized effect sizes favoring combination therapy were at least moderate in magnitude by year 2 of treatment.

■ **Figure.** Long-Term Trajectory of Cognitive and Functional Decline Is Reduced by Combination Therapy With Cholinesterase Inhibitor and Memantine[42]

A Predicted trajectory of decline over 4 years for groups of patients with AD starting with 10 errors on the BDS (~MMSE 22) is lowest in the combination therapy group.



B Predicted trajectory of decline over 4 years for groups of patients with AD starting with 25% dependence on the Weintraub ADL scale is lowest in the combination therapy group.



[a] $P < .001$ vs no medication.
[b] $P < .01$ vs ChEI monotherapy.
[c] $P < .01$ vs no medication.
[d] $P < .001$ vs ChEI monotherapy.
[e] $P < .05$ vs no medication.
AD indicates Alzheimer's disease; ADL, activities of daily living; BDS, Blessed Dementia Scale; ChEI, cholinesterase inhibitor; MMSE, Mini-Mental State Exam.
Adapted from Atri A, Shaughnessy LW, Locascio JJ, Growdon JH. *Alzheimer Dis Assoc Disord.* 2008;22: 209-221.

Lopez and colleagues compared the effects of concomitant ChEI and memantine combination therapy to treatment with a ChEI alone or no treatment at the time of nursing home admission and death.[43] Of 943 patients with AD and at least a 1-year follow-up evaluation, 140 (14.9%) used both ChEIs and memantine, 387 (41%) used only ChEIs, and 416 (44.1%) used neither. Compared with those who never used a ChEI or memantine, patients receiving ChEIs had a significant delay in nursing home admission, and this delay was significantly increased in patients who were on combination therapy. Patients taking combination therapy were 3 to 7 times less likely to be admitted to a nursing home during follow-up than those taking ChEIs alone. Importantly, ChEI treatment alone, or in combination with memantine, had no significant association with time to death. Time to death, however, was significantly associated with nursing home admission. These data infer that combination therapy may cause an expansion of the mid to late stages of disease-related disability in AD with a delay in end-stage disability and a contraction of the terminal stages of AD.

Another multiyear observational cohort study assessed the effect of persistent use of anti-AD medication therapy (ChEIs and/or memantine) on clinical measures in 641 patients with AD assessed annually.[44] A persistency index (PI), defined as total drug-use years divided by total symptom-years, was used to express cumulative drug exposure. Significantly slower rates of decline were associated with PI (with and without covariate adjustments) for MMSE ($P < .001$), Physical Self Maintenance Scale ($P < .05$), Instrumental ADL (IADL) ($P < .001$), and CDR sum of boxes (CDR-SB) ($P < .01$), and were suggested for the Baylor Profound Mental Status Examination scale ($P = .053$). Importantly, similar to Atri et al,[42] beneficial treatment effects were cumulative over time, were observed in patients with advanced disease, and were of clinically relevant magnitudes.[44] Maximally treated patients, compared with untreated patients, would experience a slower annual rate of decline equivalent to 1 point/yr on MMSE, 1.4 points/yr on IADL, and 0.6 point/yr on CDR-SB.

In the 3-year, open-label Swedish Alzheimer's Treatment Study, ChEI treatment, regardless of which agent was used, was associated with slower declines in daily function.[45]

Collectively, these studies strongly support a multifactorial approach to AD management including combination therapy.

Trends and Best Practices

Acquainting patients, families, and caregivers with a future compromised by AD is a challenging and time- and effort-intensive obligation of responsible clinicians. All those involved must have realistic expectations concerning not only disease progression, but the effects of AD medications. While a small percentage of patients may exhibit improvement with AD therapy, the realistic expectation of decline should be communicated. Adherence to therapy should be emphasized as a means to diminishing the emergence of symptoms and unwanted behaviors such as delusions, sleep/wake disturbances, wandering, and agitation that are often associated with progressive AD.[1] Optimal care includes evaluation and treatment to ensure proper nutrition, exercise, social and mental engagement, and restorative sleep; treatment of obstructive sleep apnea; cerebrovascular risk protection; avoidance of excessive alcohol; simplification of routines; shoring support; and imposition of adequate safety monitoring. It is important to sustain hope and a well-grounded appreciation for the contribution that the individual can make, her/his strengths and unique attributes, and the quality of life that remains.

Supplements including vitamin E, fish oil, and vitamin C may benefit some patients with AD, although controversy surrounds their efficacy and risks. Unless contraindicated due to bleeding diatheses, coronary artery disease, or another comorbidity, vitamin E (1000 IU twice daily) may be considered. In a randomized, double-blind, placebo-controlled study of moderately severe AD (n = 341), patients received selegiline, vitamin E, both, or placebo, and were followed for 2 years.[46] The primary outcome was time to severe dementia, loss of ability to perform ADL, institutionalization, or death. All active treatment groups had significant delays in the time to primary outcome compared with placebo. A meta-analysis suggested that low-dose vitamin E supplementation (up to 150 IU daily) is associated with less all-cause mortality but that high-dose vitamin E may be associated with a very small increase in RR of mortality (approximately 1.05).[47] However, the subgroup of patients with AD included in this study was observed to have a lower relative risk of mortality associated with high-dose vitamin E supplementation. A more recent study also supports that high-dose vitamin E supplementation is not associated with death in patients with AD.[48] Unfortunately, large RCTs have failed to support any general benefit from ginkgo biloba, high-dose vitamin B_{12}/folic acid combinations, certain omega-3 fatty acid/fish oil components/preparations, nonsteroidal anti-inflammatory drugs, and statin medications at the dementia stage of AD, at least in the short to intermediate term.

Pharmacotherapeutic Trends

Unless contraindicated due to conditions including unstable cardiac arrhythmias, uncontrolled seizures, and active peptic ulcer disease and GI bleeding, ChEI therapy should be initiated and slowly titrated to a maximal clinical or tolerated dose following AD diagnosis (**Table 2**).[12-15] For patients with moderate to severe AD, memantine can be initiated once patients have been maintained on stable ChEI therapy without adverse effects (Table 2). Memantine monotherapy can be initiated if the patient has moderate or later-stage AD; a ChEI can be added after stable memantine therapy without adverse effects has been established. This is a particularly useful strategy in patients who are sensitive to or experience GI side effects with ChEIs. In the event of marked adverse events, switching ChEIs can be suggested, and titration is not required. All patients should have their vascular risk factors managed diligently, including optimization of lipids (preferably with a statin), blood pressure, and blood sugar, and use of daily enteric-coated baby (81 mg) aspirin if not contraindicated. Screening and ongoing monitoring for anxiety and clinical depression and treatment with an antidepressant (preferably a selective serotonin reuptake inhibitor with low anticholinergic load and favorable geriatric profile such as citalopram) as indicated can benefit patients and caregivers. A thorough screening and treatment of functional deficiencies in vitamin B_{12} and thyroid function should be performed in all patients; these deficiencies are relatively common in the elderly, simple to treat, and can exacerbate AD symptoms and contribute to functional decline.

When to Start and Stop AD Therapy

The questions of when to start and when to stop AD medications are of utmost importance to clinicians, patients, and families. While "when to start" appears to be the simpler question because there are FDA indications for each drug class, this assumes that the clinician is adept at properly staging disease severity. Per the prescribing information, clinicians should start ChEI treatment in mild AD and memantine in moderate AD. Patients in the moderate stages can be started with a ChEI or memantine, and ultimately, as is the standard of care, the complementary agent should be added to the other to achieve combination therapy. The caveat is that there is no single measure of cognition, function, or behavior that accurately characterizes the disease severity stage in each patient. Staging disease severity also considers the impact on family and caregivers and change from premorbid levels. It requires a three-dimensional picture of an individual and depends on a variety of subjective factors.

Table 2. Dosing for AD Therapy[12-15]

Drug	Dose
Donepezil	Starting dose: 5 mg/day; can be increased to 10 mg/day after 4-6 weeks. Before starting donepezil 23 mg/day, patients should be on donepezil 10 mg/day for at least 3 months.
Rivastigmine	ORAL: Starting dose: 1.5 mg twice daily. If well tolerated, the dose may be increased to 3 mg twice daily after 2 weeks. Subsequent increases to 4.5 and 6 mg twice daily should be attempted after 2-week minimums at previous dose. Maximum dose: 6 mg twice daily.
	PATCH: Starting dose: apply one 4.6-mg patch once daily for a period of 24 hours.
	Maintenance dose: apply one 9.5-mg patch once daily for a period of 24 hours; before initiating a maintenance dose, patients should undergo a minimum of 4 weeks of treatment at the initial dose with good tolerability.
Galantamine	Extended release: start at 8 mg once daily for 4 weeks; increase to 16 mg once daily for 4 weeks; increase to 24 mg once daily.
	Generic: start at 4 mg twice daily for 4 weeks; increase to 8 mg twice daily for 4 weeks; increase to 12 mg twice daily.
Memantine	Starting dose: 5 mg once daily; increase dose in 5-mg increments to a maximum of 20 mg daily (divided doses taken twice daily) with a minimum of 1 week between dose increases.

AD indicates Alzheimer's disease.

There are no appropriate studies to guide when combination therapy should be withdrawn in AD. Memantine and the ChEI donepezil are also FDA-indicated for severe AD, and studies support their use even in late stages of dementia when patients require nursing home level care. It is important for clinicians, caregivers, and families to understand that the practical benefits of anti-dementia medications in very severe/late-stage AD are no longer for reducing decline in memory and other higher-level cognitive functions; these functions are no longer viable. Medications are maintained in late-stage AD to support basic psychomotor processes required to help caregivers deliver basic care involving feeding, dressing, and bathing, including the processes of movement, swallowing, and functional communication. The benefits may also extend to reducing antipsychotic usage.

In the very terminal stages of AD when personhood has disintegrated, when there is no meaningful communication or interaction, patients should not receive any care (pharmacological or otherwise) that does not have the direct goal of palliation and comfort—there is no economic, moral, scientific, or ethical reason for such interventions. The healthcare team must ensure that the patient's dignity and integrity are safeguarded in the dying process according to their lifelong wishes.

Further Therapeutic Trends

Severe agitation or aggression are prevalent NCBSs in severe AD, and can respond to atypical antipsychotics. Use of antipsychotics for NCBSs in dementia is off-label in the United States and the prescribing information carries an FDA black box warning. Clinicians should resist starting antipsychotics in patients with dementia, and only do so when strict conditions have been met, including a careful consideration of risks, benefits, side effects, and alternatives. They should only be used in selected patients on a multidisciplinary behavioral plan with stable combination therapy, and under the supervision of a dementia specialist, as antipsychotics can have detrimental effects on cognition, function, and patient safety. In general, benzodiazepines (eg, lorazepam) and medications with high anticholinergic activity (those for urinary incontinence, allergies, sleep disturbances [eg, diphenhydramine]) should be avoided. Stimulants are seldom indicated except for when patients have severe and refractory daytime somnolence.

Many elderly patients also accumulate a multitude of medications in their regimens over time, without professional review or discontinuation when appropriate. Clinicians should safely eliminate cognitively deleterious and redundant medications. For example, medications that appear on Beers Criteria should be avoided and substituted when possible.

The Effects of ChEIs and Memantine on NCBSs

ChEIs and memantine appear to produce complementary benefits on different items of the NPI scale. ChEIs potentially reduce depressive-, anxiety-, and apathy-related NCBSs,[49] while memantine may reduce symptoms in domains related to agitation/aggression, irritability/lability, and psychosis.[50] In an RCT with 290 patients with moderate to severe AD, significant differences favoring donepezil over placebo were observed on total NPI score at weeks 4, 18, and 24 ($P < .01$),

Table 3. Beneficial Effects of Anti-Dementia Treatments on NCBS Domains in AD[49,50]

Individual NPI Items	Donepezil vs Placebo[a]		Memantine vs Placebo[b]	
Delusions	+	NC	+[d]	- -
Hallucinations	+	-	- -	- -
Agitation/aggression	- -	- -	-[d]	- - -
Depression/dysphoria	++[c]	-	-	- -
Anxiety	+++[c]	NC	-	- -
Elation/euphoria	NC	NC	NC	-
Apathy	+++[c]	-	++	-
Disinhibition	NC	-	+	-
Irritability/lability	-	- - -	-[e]	- - -
Aberrant motor behavior	NC	- -	- -	- -
Nighttime behavior	+	+	-	- -
Appetite/eating	+	-	++	++

Key: + indicates level of improvement at 24 or 28 weeks; -, level of deterioration. The number of + or - signs indicates approximate degree of improvement or worsening. NC indicates no change.
[a] Individual NPI item analysis in patients given donepezil or placebo. Donepezil treatment was associated with significant benefits in the subdomains of depression/dysphoria, anxiety, and apathy.[49]
[b] Individual NPI item analysis in patients given memantine or placebo. Memantine treatment was associated with significant benefits in the subdomains of delusions, agitation/aggression, and irritability/lability.[50]
[c] $P < .05$.
[d] $P = .001$.
[e] $P = .005$.
AD indicates Alzheimer's disease; NCBS, noncognitive behavioral symptoms; NPI, Neuropsychiatric Inventory.

and particularly on the NPI sub-domains of depression/dysphoria, anxiety, and apathy/indifference (Table 3).[49]

The effects of memantine on NCBSs in moderate to severe AD (MMSE scores <20) were assessed in a post hoc analysis of pooled data (n = 1826) from six 24- to 28-week RCTs.[50] Compared with placebo, memantine significantly improved total NPI scores at weeks 12 and 24/28, as well as on the individual sub-domains related to aggression, lability, and psychosis (Table 3); these observed benefits are especially relevant to caregivers, as they are associated with rapid deterioration, early institutionalization, and increased caregiver burden. Gauthier et al also reported that memantine was associated with a significantly decreased incidence of future agitation/aggression ($P < .01$), depression/dysphoria ($P < .01$), and nighttime behaviors ($P = .05$) in patients with AD who had not suffered from these NCBSs at baseline.

Finally, Vidal et al used interrupted time-series analysis on data from a 2-year cohort of 4600 patients given memantine in the French National Healthcare System.[51] They reported a 39% to 50% increase in psychotropic use and stabilization of this use that temporally correlated with the introduction of memantine treatment; a potential psychotropic-usage-sparing effect related to memantine was postulated.

Conclusion

All patients diagnosed with AD can benefit from pharmacotherapy. Combination therapy with a ChEI and memantine is the standard of care as the illness enters the moderate and later clinical stages. Early diagnosis, education, patient and caregiver support, and initiation of care and multimodal therapies represent the best hope of minimizing the long-term trajectory of decline in cognition, function, and behavior in patients and for reducing caregiver burden. Clinicians need to effectively and compassionately communicate to patients and families that the current treatment paradigm in AD provides meaningful value; it can be expected to ameliorate current symptoms, delay and reduce emerging problem behaviors, reduce the pace of overall decline, provide palliation, and lower the impact of this illness on patients and caregivers. Although the current AD treatment paradigm does not provide a cure or a sustained reversal of symptoms, it can sustain and support important aspects of cognition, behavior, and ADL even in moderate and severe stages and delay nursing home placement without prolonging life at end-stage disease.

Author affiliations: Geriatric Research, Education, and Clinical Center (GRECC), ENRM VA Medical Center, Bedford, MA and Memory Disorders Unit & Massachusetts Alzheimer's Disease Research Center, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA.

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Address correspondence to: Alireza Atri, MD, PhD, Geriatric Research, Education, and Clinical Center (GRECC), ENRM VA Medical Center, 200 Springs Rd, Bedford, MA 01730. E-mail: atri@nmr.mgh.harvard.edu.

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