Current and Future Treatments in Alzheimer's Disease

Alireza Atri, MD, PhD[1,2]

[1] Banner Sun Health Research Institute, Banner Health, Sun City, Arizona
[2] Center for Brain/Mind Medicine, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Address for correspondence Alireza Atri, MD, PhD, Banner Sun Health Research Institute, 10515 W Santa Fe Drive, Sun City, AZ 85351 (e-mail: alireza.atri@bannerhealth.com).

Semin Neurol 2019;39:227–240.

Abstract

The foundation of current Alzheimer's disease (AD) treatment involves pharmacological and nonpharmacological management and care planning predicated on patient-centered psychoeducation, shared goal-setting, and decision-making forged by a strong triadic relationship between clinician and the patient-caregiver dyad. Food and Drug Administration (FDA) approved AD medications, cholinesterase-inhibitors (ChEIs), and the N-methyl-d-aspartate (NMDA) antagonist memantine, when utilized as part of a comprehensive care plan, while generally considered symptomatic medications, can provide modest "disease course-modifying" effects by enhancing cognition, and reducing loss of independence. When combined, pharmacologic and nonpharmacologic treatments can meaningfully mitigate symptoms and reduce clinical progression and care burden. AD pharmacotherapy first involves identification and elimination of potentially harmful medications and supplements. First line treatment for neuropsychiatric symptoms and problem behaviors is nonpharmacological and involves psychoeducation, trigger identification, and implementation, iterative evaluation, and adjustment of behavioral and environmental interventions. Intensive research efforts are underway to develop more accurate and practical AD diagnostic biomarkers and clinical tools and better therapeutics. Ongoing research studies for primary and secondary prevention of AD and clinical trials evaluating symptomatic and disease-modifying treatments in symptomatic AD are directed at diverse therapeutic targets including neurochemicals, amyloid and tau pathological processes, mitochondria, inflammatory pathways, neuroglia, and multimodal lifestyle interventions.

Keywords
- cognitive impairment
- dementia
- cholinesterase-inhibitor

Alzheimer's disease (AD), the most common cause of mid-to-late life cognitive impairment and dementia, is pathologically defined by deposits of amyloid-β ($A\beta_{42}$)-plaques and hyperphosphorylated-tau (p-tau) tangles. Complex, interacting, and incompletely understood biopsychosocial and pathological processes lead to heterogeneous AD clinical phenotypes (i.e., cognitive-behavioral syndromes related to AD). AD biopathological processes develop over one to two "preclinical" decades before symptoms manifest insidiously; this preclinical period is increasingly targeted in research and may represent the best opportunities to potentially delay or prevent onset of dementia stages of AD.[1,2]

The current treatment paradigm in Alzheimer's disease (AD) involves a multipronged approach of combining pharmacological and nonpharmacological approaches to mitigate progressive loss of cognitive and functional abilities. No new AD medications have been approved by Food and Drug Administration (FDA) since 2002 (other than a capsule preparation that combines two available medications). However, over the last decade multiple lines of evidence from randomized, double-blind, and placebo-controlled trials (RCT), and prospective long-term observational cohort studies have emerged to support the clinical effectiveness of AD medications, in mono-, or add-on-dual combination therapy to at least

Issue Theme Dementia; Guest Editor, Arash Salardini, MD

Copyright © 2019 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Tel: +1(212) 584-4662.

DOI https://doi.org/10.1055/s-0039-1678581.
ISSN 0271-8235.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Table 1 Risk factors for AD dementia

Modifiable (in early life, midlife ages 45–65 y, or later life ages > 65 y)	Nonmodifiable
Vascular risks: Diabetes (later life) Hypertension (midlife) Dyslipidemia (midlife) Metabolic Syndrome and obesity (midlife) Smoking tobacco (later life) Low physical activity (later life) Cerebral hypoperfusion Cerebrovascular injury or stroke Depression (later life) Severe head trauma or traumatic brain injury Hearing loss (midlife) Low cognitive reserve: low education, intelligence, professional or social attainment/occupation (early life and potentially midlife) Low social contact (later life)	Age Gender (female > male) Family history (first- or second-degree relative or multiple generations) Race Down's Syndrome ApoE-ε4 allele Cerebral amyloidosis–a biomarker of the AD pathological process[a]

Abbreviations: AD, Alzheimer's disease; ApoE, Apolipoprotein E.
[a]It is currently a nonmodifiable risk factor but primary and secondary prevention trials utilizing amyloid-modifying drugs are in progress and early results support that cerebral amyloid plaque burden can be lowered; whether this translates to clinical benefit or of lowering risk of progression to MCI or dementia, potentially making this be a modifiable risk factor, is to be determined.

modestly (with small to medium effect sizes) mitigate symptoms and retard the expected trajectory of progressive decline.[3]

The last decade has brought several major advances involving explication of AD risk factors (see ►**Table 1**) and AD diagnostics. In vivo AD biomarkers of the pathological process are now available in the clinic. Measurements of amyloid-Beta$_{42}$ (Aβ_{42}), tau (τ), and phospho-tau (p-tau) proteins in cerebrospinal fluid (CSF), as well as Aβ_{42}-plaque burden on amyloid-PET (positron emission tomography), can now aid clinical, as well are research, diagnosis of AD with a high level of certainty. Though breakthroughs to affect newer AD therapeutics have yet to materialize, learning from dozens of large and varied clinical trial programs have provided cornerstones of ongoing intensive research efforts that aim at primary and secondary prevention, as well as symptomatic and disease-modifying treatments for AD.

This paper will (1) review current multifactorial management of AD, with a focus on practical aspects of psychoeducation and behavioral approaches, clinical evidence, and considerations for treatment with FDA-approved AD medications; and (2) briefly summarize experimental pharmacological approaches under research investigation that are likely to form the bases of future combination therapies in the AD clinical spectrum.

Current Treatments in AD

There is no cure for AD dementia. It is increasingly recognized that the complex and incompletely understood pathological processes culminating in AD dementia can begin decades prior to the manifestation of clinical symptoms, by which time extensive and likely irreversible processes have wrought widespread destruction on multiple levels: molecular, intracellular, cellular, network, and systems. The current AD treatment paradigm is one of multifaceted management of symptoms aimed at retaining quality of life, mitigating the burden of illness and reducing long-term clinical decline. Successful long-term pharmacotherapy with FDA-approved AD medications, initially involving monotherapy with a cholinesterase-inhibitor (ChEI) and ultimately involving add-on dual-combination treatment with a ChEI and memantine, requires developing, implementing and sustaining a solid foundation of psychoeducation, nonpharmacological and behavioral care strategies, and clarity in care goals and expectations; this is predicated on a strong therapeutic alliance between the clinician and the patient–caregiver dyad.

Management of AD

►**Table 2** broadly outlines the multifactorial tailored management of AD. Evaluation and management of AD requires a solid foundation of open, honest, and compassionate communication; shared goal setting; and a triadic partnership between the clinician, patient and care-partner(s). Evaluation and management should be a patient–caregiver dyad-centered and dynamic processes that involve multipronged and, ideally, integrated interdisciplinary team approaches. Treatment of AD is not curative and successful management to mitigate the burden of illness relies on four basic pillars: (1) timely and accurate syndromic and etiological diagnoses combined with proactive educational and care planning that are customized to the patient–caregiver dyad (the dyad)–without accurate diagnosis and tailored psychoeducation, appropriate dyad-centered treatment, and care can't be provided; (2) nonpharmacological interventions and behavioral approaches; (3) pharmacological interventions; and (4) holistic care planning that is proactive, pragmatic and dynamic, and includes monitoring and adjustment of the

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Table 2 Key Elements of effective multifactorial management of AD

Patient-caregiver dyad-centered evaluation, diagnosis and disclosure, and care planning processes
• Timely detection of symptoms, accurate assessment and diagnosis, iterative psychoeduction, and appropriate disclosure.
• Shared goal setting for diagnostic, disclosure and management processes; sustained psychoeducation and tailoring of a proactive care plan to patient-caregiver dyad.
Nonpharmacological management: interventions and behavioral approaches and strategies:
• Psychoeducation including regarding AD dementia in general and effects on cognition, function and behaviors, dementia care, expectations, "the progression and regression model of aging and dementia."
• Behavioral approaches and strategies–both general and targeted to the patient-caregiver dyad; these include simplification of environment, establishing routines, providing a safe, calm, and consistent care environment, utilizing strategies such as interacting calmly, redirection to pleasurable activities and environment, reassurance, providing only necessary information in a manner that the patient can appreciate (i.e., in simple language and small chunks) and at the appropriate time, "benign therapeutic fibbing" and "never saying no" (unless immediate safety is concerned) to "allow the moment to pass."
• Establishing and fostering support networks for the patient and caregivers.
• Identifying and monitoring health and safety risks for patient and others, advance planning for medical, legal, and financial decision-making and needs (e.g., stove, weapon, and driving safety; falling prey to fraud or poor work or financial decision making).
• Caring for caregivers, including caregiver support and respite care.
Pharmacological management:
• Elimination of redundant and inappropriate medications (Beers's criteria);
• Treating underlying medical and psychiatric conditions, and associated symptoms that can exacerbate cognitive-behavioral impairment/dementia (e.g., dehydration, pain, constipation, infections, electrolyte and metabolic derangements, anxiety, depression, psychosis).
• Prescription of stage-appropriate FDA-approved AD medications (ChEI's: donepezil, rivastigmine, galantamine; NMDA-antagonist: memantine) as monotherapy or add-on-dual combination therapy (ChEI + memantine).
Pragmatic modifications to sustain alliance, adherence and well-being of patient-caregiver dyad
• Flexibility to modify care plan according to important changes in the patient-caregiver dyad.
• Forging and sustaining a therapeutic alliance.
• Promoting the safety, health and well-being of the patient and her/his caregivers.
• Adopting a pragmatic approach to ongoing care that includes establishing and simplifying care routines where possible, modifying the environment to suit the patient-caregiver dyad, and consideration of patient and caregiver preferences, capacity, environment and resources in devising and implementing care plans.

Abbreviations: AD, Alzheimer's disease; ChEI, cholinesterase-inhibitors; FDA, Food and Drug Administration; NMDA, N-methyl-d-aspartate.

care plan according to the dyad's goals, capacity, condition, and resources.

Psychoeducation

Management of AD should foremost involve dyad-tailored psychoeducation based on the dyad's priorities, strengths and limitations, environment, and resources. These factors are also salient during the evaluation process and in recommending, implementing, monitoring, and adjusting nonpharmacological and pharmacological interventions, and in the execution of a successful care plan. Psychoeducation should also iteratively, throughout the evaluation and management processes, assess the understanding (knowledge of facts) and appreciation (recognition that facts apply to the person) regarding the presence, severity, and functional effects of the symptoms, the clinical syndrome, and the underlying condition/disease (e.g., AD), and regarding care plans. These factors guide education and communication that should be part of a structured process and dialogue to inform the dyad regarding the patient's clinical status (e.g., mild cognitive impairment vs. dementia); syndromic diagnosis (e.g., multidomain amnestic dementia with language and executive dysfunction); etiological diagnosis (i.e., underlying cause(s), such as AD or multiple etiology (mixed) dementia due to AD, and vascular cognitive impairment); expected course; life, safety-related and care planning needs; treatment, support, and care options; and health system, public, and psychosocial resources. Once this foundation is formed, a stage-appropriate pharmacological treatment plan can be instituted. Long-term dyad-centered management of AD requires proactive planning and flexibility to monitor and modify care plans according conditions, resources, and goals.

NonPharmacological Management

Behavioral problems, strategies, and interventions: during the course of illness, 85 to 90% of patients with AD will experience significant neuropsychiatric symptoms and problem behaviors (namely, noncognitive behavioral symptoms [NCBS]; or behavioral and psychological symptoms of dementia [BPSD]), and BPSD are associated with more rapid decline, earlier

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

institutionalization, higher distress, worse quality of life, and greater health care utilization and costs.[4,5] Nonpharmacological interventions and behavioral strategies are the first line option to ameliorate neuropsychiatric symptoms (e.g., agitation, apathy, delusions, disinhibition) and problem behaviors (e.g., resistance to care, caregiver shadowing, hoarding, obsessive-compulsive behaviors) in AD dementia.[6,7] BPSD are distressing to patients and caregivers and left untreated, their chronic effects exact a large toll and lead to poor outcomes for patients and caregivers.[4,5] Treatment of BPSD using pharmacological interventions alone has low efficacy with small Cohen's d effect sizes of 0.2 or less; and in some cases, such as with antipsychotics, is associated with risks of substantial side effects, and short and long-term morbidity and mortality.[8]

Structured BPSD assessment, root-cause analysis, mitigation, monitoring, and care plan modification are important components of a comprehensive AD dementia care plan; they can facilitate prevention and mitigation of BPSD by eliminating triggers and directing treatments to the root cause, not just directed at the symptoms. Precipitating factors for specific behavior (e.g., triggers for a specific BPSDs) should be identified, modified, and continually assessed. Nonpharmacologic interventions and behavioral strategies against BPSD include both general and tailored approaches to caregiver psychoeducation and training in dementia-specific strategies for trigger avoidance, problem solving, communication, environment modification, task simplification, and "just right" patient engagement and activities.

BPSD psychoeduction for caregivers should include some explanation of general models of the biopsychosocial substrates of BPSD in AD, such as loss of behavioral and coping reserve, compromise of "top–down" control in frontostriatal networks, progression–regression models of aging and dementia with stripping of control systems and degenerative regression to early developmental stages in which limited capacities drive perceptions and problem behaviors. It is important to explain to caregivers that poor or problem behaviors by the individual with AD dementia are not intentional (e.g., to be mean, ornery, or vindictive) but are due to disease, brain injury/damage, and diminished capacities.

Pharmacological Management

The current AD medication treatment paradigm is to reduce progression of symptoms and disability; expectations are for pharmacological treatments to modestly retard expected clinical decline in ways that are nonetheless meaningful. Despite ongoing efforts, a magic bullet or "cure" for AD in the dementia stages is unrealistic in the near future; by the time AD is in the dementia stages, degeneration has wrought multilevel brain destruction for one or more decades. Combined together, nonpharmacologic and pharmacologic management in AD seek to minimize the disabling effects of cognitive and functional decline and emergence and severity of BPSD. The FDA-approved AD medications, the ChEI's donepezil, galantamine, and rivastigmine, and the N-methyl-d-aspartate (NMDA) antagonist memantine, can reduce progression of clinical symptoms and disability. From a public health and economics perspective, therapies that minimize caregiver burden and delay nursing home entry translate into significant benefits related to worker productivity and health care savings.[9–12]

Review and elimination of potentially deleterious medications: the initial step in the pharmacologic management of AD consists of reviewing and eliminating redundant and potentially deleterious medications. For example, diphenhydramine, often taken as an over-the-counter drug combination with acetaminophen for sleep and pain relief, and medications for anxiety (e.g., benzodiazepines), urinary incontinence (e.g., those with high anticholinergic activity), and sedative/hypnotics are relatively contraindicated in the elderly, require close scrutiny, and can be particularly deleterious in cognitively vulnerable older persons (see Beers's criteria)[13,14]

Treatment of co-morbid conditions that may contribute to or decompensate dementia symptoms: identifying and treating conditions that can negatively impact cognition, function, and behavior in patients with AD can substantially affect clinical outcomes. In many individuals, the symptoms and signs of decompensation can be subtle, chronic, and may not manifest as acute delirium/encephalopathy (see[15,16] for a review of delirium-dementia link). A cognitive laboratory panel (e.g., complete blood count [CBC], complete metabolic panel with liver panel, thyroid stimulating hormone [TSH], vitamin B_{12}, homocysteine, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) can help to identify common conditions that may exacerbate cognitive or behavioral decline, including dehydration, electrolyte and metabolic derangements, anemia, cardiac or cerebral ischemia, hypoxia, thyroid and vitamin deficiencies (e.g., vitamin B_{12} deficiency), and infections (e.g., urinary tract infections, pneumonia). Other conditions, such as pain, for example, from arthritis, constipation, hunger, thirst, and fatigue are also common in AD, particularly in later stages when patients cannot appropriately recognize or communicate their symptoms; these can lead to BPSD, particularly anxiety, irritability, agitation, aggression, and sleep-wake disturbances.

Use of antipsychotics in ad is off-label and carries substantial risk. Antipsychotics must be used with extreme caution, with ongoing monitoring and only when strict conditions have been met.[8,17] In the U.S., though commonly used as off-label, antipsychotics carry an FDA black-box warning in dementia. Short- and long-term antipsychotic use in patients with dementia is associated with substantial risk of cognitive decline, morbidity (e.g., parkinsonism, falls, pneumonia, cardiovascular, and cerebrovascular events), and mortality. Antipsychotics should only be used as a last resort for severe refractory behavioral disturbances without an identifiable and treatable cause (e.g., severe aggression, agitation, or psychosis not due to delirium, pain, or infection) or when a serious risk of immediate harm or safety exists that cannot be otherwise ameliorated.[8,17] Risperidone is approved by the European Medical Agency (EMA) for short-term, 12-week, use in dementia when there is refractory severe agitation or psychosis; it is not approved for this indication in the U.S. After a careful evaluation, ideally by a dementia subspecialist, cautious use of antipsychotics should be limited to the lowest effective dosages for short durations; continued use requires ongoing monitoring, assessment of risk-benefit, and understanding,

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

and continued consent from the family/care providers regarding the goals of treatment, and the potential clinical trade-offs.

FDA-Approved AD Medications: ChEIs and Memantine

ChEIs (donepezil, galantamine, rivastigmine) and the NMDA antagonist, memantine, are the only FDA-approved treatments for AD dementia, and are recommended broadly in consensus guidelines and practice parameters.[1,7,18,19] The ChEIs and memantine have complementary mechanisms of action, potentially additive effects, and demonstrate acceptable tolerability and safety profiles.[20] A recent systematic review and meta-analysis by Tricco et al that included 110 studies and 23,432 patients also further supports efficacy, effectiveness, and safety of these AD medications.[3] A pharmacological foundation of AD therapies whether with ChEI or memantine monotherapy, or ultimately combined together as add-on-dual combination therapy, most often as memantine added-on to stable background ChEI treatment have demonstrated benefits in the short- and long-term to reduce decline in cognition and function, retard the emergence and impact of neuropsychiatric symptoms, and delay nursing home placement without prolongation of time to death.[3,21] From a public health perspective, AD pharmacotherapy (donepezil, memantine, galantamine, rivastigmine) can reduce the economic burden of the illness, even in the later stages of illness.[10]

Short-term responses to AD medications vary between individuals. Aggregate data supports that during the initial 6 to 12 months of treatment, performance on measures of cognition, activities of daily living (ADLs), behavioral symptoms, or global clinical impression of change may significantly improve in a minority (10–20%), plateau in nearly half (30–50%), or continue to deteriorate in about a third (20–40%) of treated patients. In dementia stages of AD, the number needed to treat (NNT) to achieve stabilization or improvement in one or more clinical domains (e.g., cognition, function, behavior, global severity) ranges from 5 to 9:1 for monotherapy (with ChEI or memantine), as well as for dual ChEI-memantine add-on combination therapy.[22–24] The NNT to achieve significant improvement on multiple domains simultaneously is approximately 8:1 for ChEI-memantine dual combination therapy in moderate to severe AD; in contrast, marked clinical worsening, defined by simultaneous significant worsening on multiple domains, is also reduced by 48 to 68% with ChEI-memantine combination therapy compared with ChEI alone.[20] At the group level in clinical studies, discontinuation of ChEI treatment has been demonstrated to be harmful–the group of patients taken off and the group of patients that are noncompliant with medication adherence appear to progress more rapidly than groups of patients who continue treatment. Unless otherwise indicated, clinicians should avoid discontinuation trials of ChEIs to "see if there is worsening"–even temporary discontinuation is associated with irreversible declines and greater risk of nursing home placement.[25–30] The question of when, in whom, and how to discontinue AD medications (e.g., deprescription), particularly in late-stage dementia, requires further research.

Sustained AD medication treatment provides greater likelihood of overall stabilization in the short-term and an expected modest reduction in the trajectory of clinical decline in the long-term. As the AD progresses, over several months to years, patients who may initially show improvement or stability, will eventually decline, even when pharmacological treatments are sustained. The care plan for any individual patient should be holistic, evidence-based, and customized to dyad goals, preferences, and circumstances. It is important for clinicians to communicate practical issues and expectations associated with AD pharmacologic treatment; these include treatment rationale and expected outcomes. In the long run, current pharmacological management of AD can mitigate but not prevent decline.

Cholinesterase-inhibitors: ChEIs facilitate central cholinergic activity by reducing the physiological breakdown of acetyl Ch (ACh) by the enzyme acetylcholinesterase (AChE) in the synaptic cleft. Inhibition of AChE by ChEIs thus enhances cholinergic neurotransmission.

Pharmacokinetics and characteristics: although there are mechanistic and pharmacokinetic differences among the available ChEI drugs (see ►**Table 3**), there is no compelling data to support significant group-level efficacy differences between them. An oral formulation of all three ChEI's is generically available in the U.S. Donepezil and rivastigmine have approved FDA-label indications in mild, moderate, and severe AD dementia; galantamine is FDA-approved for mild and moderate AD.

Table 3 Pharmacokinetic and mechanistic characteristics of the AD dementia ChEI's: donepezil, rivastigmine, rivastigmine transdermal patch, galantamine, and galantamine extended-release

Drug	Half-life (h)	T_{max} (h)	Hepatic metabolism	Absorption affected by food	Reversible inhibition of AChE
Donepezil	60–90	3–5	Yes	No	Yes
Rivastigmine	1.5–2[a]	0.8–1.8	No	Yes	No[b]
Rivastigmine Patch	3.4[a]	8–12	No	No	No[b]
Galantamine	5–8	0.5–1.5	Yes	Yes	Yes
Galantamine ER	25–35	4.5–5	Yes	Yes	Yes

Abbreviations: AChE, acetylcholinesterase; AD, Alzheimer's disease; BuChEI, butyrylcholinesterase inhibitor; ChEI, cholinesterase-inhibitors; Galantamine ER, galantamine extended-release capsules; T_{max}, time to maximum plasma concentration.
[a]Rivastigmine has plasma half-life of 2–3.4 hours but a duration of action for AChE inactivation of 9 hours.
[b]Rivastigmine is a "pseudo-irreversible" inhibitor of AChE and BuChE.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

ChEIs safety and tolerability: with slow titration in appropriate individuals, ChEIs are generally tolerated well and have an acceptable adverse effect profile.[3] The most common adverse effects which include nausea, vomiting, anorexia, flatulence, loose stools, diarrhea, salivation, and abdominal cramping are related to peripheral cholinomimetic effects on the gastrointestinal (GI) tract. For oral preparations, adverse GI effects of ChEIs can be minimized by administering the drug after a meal or in combination with memantine. Some individuals can experience vivid dreams or mild insomnia, thus doses should ideally be given after a meal in the morning. The rivastigmine transdermal patch can also cause skin irritation, redness, or rash at the site of application. Overall, adverse effects may occur in 5 to 20% of patients starting on ChEI's but are usually mild and transient, and can be mitigated by dose and rate of dose escalation. ChEIs may also decrease heart rate and increase the risk of syncope, particularly in susceptible individuals (e.g., those with sick sinus syndrome or atrioventricular [AV] block) and with overdose. Use of these agents is contraindicated in patients with unstable or severe cardiac disease, uncontrolled epilepsy, unexplained syncope, and active peptic ulcer disease. Risk of adverse effects can also be mitigated by supervising administration of all medications, including ChEIs–too often patients with AD, particularly in milder stages, are left unsupervised to access or take medications, resulting in inconsistency or duplication of doses; this can substantially affect efficacy and induce harm.

ChEIs efficacy and effectiveness: In over 40 short-term randomized placebo-controlled trials (RCTs) over 24 to 52 weeks investigating efficacy, and in meta-analyses of RCTs, all three ChEIs have demonstrated small to medium effect-size treatment benefits at the patient-group level in terms of improving, stabilizing or delaying decline in cognition, activities of dialing living, and global status, and in ameliorating BPSD and caregiver burden.[21,28,29,31–43] In the few studies that have directly compared ChEIs to each other, no significant differences were found.[44,45] Longer term benefits of 2 to 4 years or more are also supported by longer term open-label extension[27,46–48] and long-term prospective observation clinical cohort studies.[49–53]

Level II (and equivocal level I) evidence suggest donepezil may be beneficial in very mild stage AD or for subgroups with mild cognitive impairment (MCI) due to AD (i.e., carriers of APOE-e4 (Apolipoprotein E) allele,[54] those with depression or depressive symptoms[55]). Such off-FDA label pharmacotherapy is not sufficiently supported by level I evidence to warrant an unequivocal recommendation for all patients. However, efficacy/effectiveness, risk (tolerability and safety), and cost data, individual clinical circumstances, and patient-caregiver dyad preferences may warrant a discussion between clinicians, patients, and caregivers about this possibility.[54]

NMDA antagonists (memantine): Memantine was the last FDA-approved treatment for AD dementia (2002) and remains the sole medication in its class. Memantine affects glutamatergic transmission; it is a low to moderate affinity NMDA-receptor open-channel blocker.

Memantine pharmacokinetics and characteristics: Memantine is available in immediate-release twice daily (available generically in the U.S.) and extended-release once daily preparations. A combination capsule that combines donepezil 10 mg with various dosages of memantine extended-release (XR) is also available in the U.S. The pharmacokinetic profiles and characteristics of the memantine formulations are reviewed in ►**Table 4**. Memantine is mostly renally cleared and does not affect the hepatic CYP450 enzyme system.

Memantine safety and tolerability: titrated appropriately, memantine has a favorable safety and tolerability profile. Mild and transient treatment-emergent side effects may include confusion, dizziness, constipation, headache, and somnolence; these may be encountered during, or soon after, titration to the maximum total daily dose of 10 mg twice daily for immediate-release memantine, or 28 mg once daily for memantine XR. In patients with significant renal insufficiency (creatinine clearance < 30 mL/min), a dose-adjustment to 5 mg twice daily for immediate-release memantine and 14 mg daily for memantine XR is recommended.

Memantine efficacy and effectiveness: Memantine is FDA-approved for the treatment of moderate to severe AD dementia, as monotherapy or in combination with a ChEI (often added on to existing ChEI treatment). In moderate and severe stage AD

Table 4 Pharmacokinetic characteristics and effects of the AD dementia voltage-dependent, low affinity, open-channel NMDA blockers: memantine and memantine extended-release

Drug	Half-life (h)	T_{max} (h)	Hepatic Metabolism	Renal Excretion	Absorption Affected by Food	Other notes
Memantine	60–80	9–12	Little ($< 10\%$)[a]	Yes[b]	No	10 mg twice daily max dose (20 mg total daily max)[d]
Memantine XR	60–80	18–25[c]	Little ($< 10\%$)[a]	Yes[b]	Yes[c]	28 mg once daily max dose[d]

Abbreviations: AD, Alzheimer's disease; Memantine XR, memantine extended-release capsules; NMDA, N-methyl-d-aspartate; T_{max}, time to maximum plasma concentration.

[a]Memantine does not significantly inhibit the CYP450 hepatic enzyme system.

[b]Renal excretion is the main factor for memantine elimination - maximum dosages are halved in individuals with CrCl < 30.

[c]Memantine XR absorption is slower after food than on an empty stomach; peak plasma concentrations are achieved 18 hours on an empty stomach and 25 hours after food.

[d]Memantine XR affects a slower release compared with memantine and a potentially higher target dose (compared with twice-daily 10-mg dosing of immediate-release memantine it achieved a 48% higher steady-state maximum plasma concentration (C_{max}) and 33% higher area under the plasma concentration– time curve from time 0 to 24 hour (AUC0–24))

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

dementia, the short term efficacy of memantine monotherapy over treatment with placebo has been demonstrated in several RCTs of 12 to 50 weeks duration and supported by meta-analyses; these treatment benefits include improvement, stabilization, or reduced decline in the domains of cognition, function (ADLs), and global status, and by amelioration of BPSD and caregiver burden.[9,20,22,23,29,56–67] Short-term (6 months or less) memantine treatment effect sizes are small to medium in size and clinically significant at the moderate to severe stages of AD.[22,66,68,69] However, effect sizes associated with memantine treatment may be smaller and not readily detectable in mild AD, particularly over short durations of treatment.[20,34,56,70–72] Yet, the practice of off-label prescription of memantine, most often in combination with a ChEI, in patients with mild AD is common, particularly in patients who are younger or may have faster progression, and has been criticized as unsupported by some.[73,74] Nonetheless, long-term prospective observational clinical patient cohort studies have reported reduced clinical decline in patients with AD who are treated at any stage of the illness.[75–80]

ChEI and memantine add-on dual combination treatment: several types and grades of clinical data, including those from short-term (6–12 months) RCTs (level I evidence), longer-term (12–36 months) open-label extensions to RCTs (level II/III evidence), and from long-term (2–5+ years) observational prospective clinical cohort effectiveness studies (level II evidence) support the safety and benefits of AD treatments in combination–most frequently as memantine added on to a stable regimen of background ChEI treatment.[75–80] Systematic reviews and meta-analyses also provide level II grade evidence for the benefits of ChEI-memantine add-on combination treatment in AD dementia.[3,20,21,34,36,81–83]

Efficacy in short-term randomized, double-blind, placebo-controlled trials: three 24-week, randomized, double-blind, RCTs have investigated the efficacy and safety of memantine 20 to 28 mg/day in combination with a ChEI.[72,84] Two of these trials were conducted with patients in the moderate to severe range of AD severity and were successful in demonstrating efficacy on multiple prespecified outcome measures.[84] Another study conducted in patients in the mild to moderate AD severity range failed to demonstrate statistically significant results on prespecified outcomes and is considered an underpowered and indeterminate study by some.[20,72] All three studies demonstrated overall good tolerability and safety for combination treatment compared with chronic baseline ChEI monotherapy.

Safety and tolerability of ChEI-memantine add-on combination treatment: several studies have reported on safety and tolerability of combination therapy; overall, there is a good profile for both. Addition of memantine to stable doses of ChEIs does not correspond to significant overall increases in adverse events (AEs). The rates of discontinuation due to AEs for ChEIs and memantine combination treatment are low (see ►**Table 5**), between 5 to 10%, and not generally significantly different from placebo.[58,72,84–86]

Vitamins, medical foods, and supplements: Other than for vitamin E, large RCTs have failed to provide support from level III/IV epidemiological association studies for potential benefit of vitamins/supplements at the AD dementia stage. Unless contraindicated due to bleeding diatheses, coronary artery disease, or another comorbidity, high-dose vitamin E (1,000 international units twice daily was the regimen tested) may be considered based on results of two RCTs that supported an approximately 20% lower rate of ADL

Table 5 Comparison of adverse events (AEs) with an incidence $\geq$ 5% between AD treatment groups; incidence of AEs over 24 weeks was similar between the patients treated with memantine added to donepezil versus placebo added to donepezil[20]

Adverse event	Moderate and Severe AD MMSE< 20 (5–19)[a]		Moderate AD MMSE 10–19[b]	
	Memantine added to donepezil (n = 269)	Placebo added to donepezil (n = 251)	Memantine added to donepezil (n = 190)	Placebo added to donepezil (n = 185)
Patients with AEs	206 (76.6)	186 (74.1)	144 (75.8)	136 (73.5)
Dizziness	20 (7.4)	19 (7.6)	17 (8.9)	16 (8.6)
Agitation	17 (6.3)[c]	29 (11.6)	9 (4.7)[c]	19 (10.3)
Confusional state	15 (5.6)	6 (2.4)	–	–
Diarrhea	14 (5.2)	21 (8.4)	12 (6.3)	14 (7.6)
Nasopharyngitis	14 (5.2)	6 (2.4)	–	–
Falls	11 (4.1)	15 (6.0)	10 (5.3)	11 (5.9)
Urinary tract infection	–	–	10 (5.3)	8 (4.3)
Depression	–	–	6 (3.2)	11 (5.9)

Abbreviations: AD, Alzheimer's disease; APT, all-patients-treated; AE, adverse event; MMSE, mini-mental state examination.
Data are number (%).
[a]Moderate to severe AD (MMSE 5–19 at baseline), receiving donepezil (10 mg/day).
[b]Moderate AD (MMSE 10–19 at baseline), receiving donepezil (10 mg/d).
[c]$p < 0.05$ versus placebo added to donepezil.
"–" denotes AEs with an incidence < 5% in both treatment groups in the respective severity subgroup.
Note: Agitation was reported less in patients taking memantine add-on-to-donepezil dual combination treatment than in those on background donepezil monotherapy

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

decline over 2 to 3 years; there were no concerning safely signals or increased mortality with high-dose vitamin E.[87,88] There is no compelling evidence that Souvenaid, a prescription nutritional supplement (namely medical food), containing Fortasyn Connect, provides additional benefits in patients with AD dementia treated with AD medications.[89] Unfortunately, large RCTs have also failed to support benefits from ginkgo biloba, high-dose vitamin B_{12}/folic acid combinations, omega-30-fatty acid/fish oil components/preparations, nonsteroidal anti-inflammatory drugs, and statin medications at the dementia stage of AD.[31,37]

Practical recommendations for pharmacological management: unless contraindicated due to conditions including unstable cardiac arrhythmias, uncontrolled seizures, active peptic ulcer disease, and GI bleeding or unexplained syncope, ChEI therapy should be initiated following diagnosis of AD dementia and slowly titrated over months to years to a maximal clinical or tolerated dose (see ►**Table 6**). For patients with moderate to severe AD, memantine can be initiated once patients have received stable ChEI therapy for several months without adverse effects (►**Table 5**). Memantine monotherapy can be initiated on-label if the patient has moderate or later stage AD; conversely a ChEI can be added after several months of stable memantine monotherapy. The latter may be a particularly useful strategy in patients who are very sensitive to or experience GI side effects with ChEIs. A very low and slow titration (e.g., starting donepezil 2.5 mg daily after breakfast, increasing it to 5 mg daily if no side effects emerge within 6 weeks) may be helpful in patients who are very sensitive to cholinomimentic effects. In highly refractory situations, switching to another ChEI at a low-dose can be tried. Persistence, higher dose (in later dementia stages) and duration of treatment are associated with better outcomes even in those with advanced dementia.[50,53,75,76,90]

All patients should have diligent management of their vascular risk factors including lipids, blood pressure, and glucose. Anxiety and clinical depression should be monitored and treated (using a selective serotonin reuptake inhibitor [SSRI] with low anticholinergic load and a favorable geriatric profile, e.g., citalopram, escitalopram, sertraline). There should be proactive monitoring and optimization of sleep, stress level, hydration, and nutrition status; any deficiencies (e.g., thyroid, vitamin B_{12}) and systemic conditions that can decompensate mental functions should be treated (e.g., urinary tract infection [UTI], dehydration, hyponatremia). Along with social and mental engagement, and stress management, daily exercise, and physical activity should be an integral part of the care plan.

Potentially deleterious medications, including anticholinergic medications and benzodiazepines, should be weaned off and avoided. Off-label use of antipsychotics should be

Table 6 Recommended dosing for FDA-approved AD medications: ChEIs donepezil, rivastigmine and galantamine; and NMDA-antagonist memantine

Drug	Dose and notes
Donepezil	Starting dose: 5 mg/d; can be increased to 10 mg/d after 4–6 wk. Before starting donepezil 23 mg/d, patients should be on donepezil 10 mg/d for at least 3 mo.
Rivastigmine	Oral: Starting dose: 1.5 mg twice daily. If well tolerated, the dose may be increased to 3 mg twice daily after 2 wk. Subsequent increases to 4.5 and 6 mg twice daily should be attempted after 2 wk minimums at previous dose. Maximum dose: 6 mg twice daily. Oral rivastigmine can be difficult to tolerate.
	Patch: Starting dose: one 4.6 mg patch once daily for a period of 24 h. Maintenance dose: one 9.5 mg or 13.3 mg patch once daily for a period of 24 h. Before initiating a maintenance dose, patients should undergo a minimum of 4 wk of treatment at the initial dose (or at the lower patch dose of 9.5 mg) with good tolerability.
Galantamine	Extended-release: Start at 8 mg once daily for 4 wk; increase to 16 mg once daily for 4 wk; increase to 24 mg once daily.
	Generic: start at 4 mg twice daily for 4 wk; increase to 8 mg twice daily for 4 wk; increase to 12 mg twice daily.
Memantine	Immediate-release: 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 wk between dose increases. In earlier stages may consider 10 mg daily dose. The maximum recommended dose in severe renal impairment is 5 mg twice daily. Extended-release (XR): for patients new to memantine, the recommended starting dose of memantine XR is 7 mg once daily, and the recommended target dose is 28 mg once daily. The dose should be increased in 7 mg increments every 7th d. The minimum recommended interval between dose increases is one week, and only if the previous dose has been well tolerated. The maximum recommended dose in severe renal impairment is 14 mg once daily.
Memantine XR/ donepezil capsule (branded combo capsule)	Combination capsule consisting of 7–28 mg memantine/10 mg donepezil given orally once daily. Can be started in patients already on background stable donepezil 10 mg daily (with memantine dose titration) or in patients already on combination treatment with each agent. The maximum recommended dose in severe renal impairment is 14 mg memantine XR/10 mg donepezil once daily.

Abbreviations: AD, Alzheimer's disease; ChEI, cholinesterase-inhibitors; FDA, Food and Drug Administration; NMDA, N-methyl-d-aspartate; Memantine XR, memantine extended-release capsules.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

used with great caution and only under specific circumstances when behavioral/environmental interventions have failed, and after careful consideration of risks, benefits, side effects, and alternatives.[17] Stimulants are seldom indicated and may lower threshold for irritability, agitation/aggression, and dysphoria.

When to start and stop AD medications: per FDA prescribing information, clinicians may start a ChEI in mild, moderate, or severe AD, and memantine in moderate or severe AD. In moderate stages, a ChEI or memantine can be started, and ultimately, the complementary agent can be added to achieve dual/combination therapy. Based on the patient–caregiver dyad preferences and clinician comfort and expertise, an individualized discussion can be prompted regarding the pros and cons, cost, and uncertainties of off-label prescription of AD medications, such as ChEIs in MCI due to AD[54] and high-dose vitamin E.[87,88]

AD medications can be maintained in late-stages to support basic psychomotor processes, praxis, functional communication, behavioral responses required to assist caregivers to deliver basic ADL care, and the elementary processes of movement and eating. The benefits may also extend to reducing antipsychotic usage. In the terminal stages of AD when personhood has disintegrated, and when there is no meaningful communication or interaction, patients should only receive care (pharmacological or otherwise) that is directed to provide palliation and comfort.[91]

Future Treatments in AD

Despite no new treatments being approved for AD since 2002, and the failure or abandonment of more than 200 investigational programs in the interim, the AD drug pipeline remains moderately full of presumed disease-modifying and symptomatic agents with a variety of mechanisms of action (MOA). A search of *clinicaltrials.gov* (accessed November 19, 2018) for phase I–III interventional clinical trials that are "recruiting" or "active but not recruiting" for AD shows over 150 results. A recent annual review of the AD drug development pipeline found 112 agents: 26 agents in 35 trials in phase III, 63 agents in 75 trials in phase II, and 23 agents in 25 trials in phase I.[92] The presumed MOA of agents in the pipeline were classified as disease-modifying therapies (DMT) in 63%, symptomatic cognitive enhancers in 22%, and symptomatic agents addressing BPSD in 12%.[92]

Agents classified as DMTs are posited to affect upstream underlying AD pathobiology related to Aβ and tau, and are hypothesized, if efficacious, to be able to slow disease progression that would manifest clinically with chronic benefits (over many months to years) of reducing the rate of decline. Agents classified as symptomatic therapies are posited to mainly affect downstream neurochemical, molecular, synaptic, physiological or network-level dysregulation caused by AD pathobiology and resultant disruptive cascades, and are hypothesized to be able to show symptomatic effects that would manifest clinically with relatively acute benefits (over weeks to a few months) of improvement in cognitive functions or mitigation of symptoms.

While DMTs are presumed to affect AD etiology, this area remains one of controversy and one that is not completely understood.[93–95] Over the past 25 years, variations of prevailing "amyloid-related" hypothesis models of AD have posited a causative or necessary role of accumulation of synapto- and neuro-toxic forms of Aβ, namely $A\beta_{42}$ oligomers, protofibrils, and fibrils, ultimately forming insoluble extracellular plaques to induce inflammatory and microglial cascades, broad ionic and neurotransmitter abnormalities, mitochondrial dysfunction, oxidative stress, and hyperphosphorylation of the microtubule stabilizing protein tau, and formation of tangles.[95–100] tau-Mediated processes are posited to cause further synaptic and neuronal dysfunction and destruction, suggested to have a prion-like seed and spread intersynaptically and interneuronally, thus leading to widespread cortical dysfunction. Other models have posited microvascular injury tipping the balance in favor of accumulation of toxic $A\beta_{42}$ species,[94] and two-stage models that posit an "amyloid-dependent" first phase, led by soluble oligomeric and fibrillar Aβ accumulation that over time becomes increasingly decoupled from amyloid in the "amyloid-independent" second stage to cause further neurofibrillary tangles (NFT) formation, neuronal and synaptic loss and further sequelae.[95]

Support for an early and central role of Aβ in AD pathogenesis comes from a rare familial autosomal dominant forms of AD (FADAD; accounts for $< 1\%$ of all AD) that usually manifest in "early-onset" AD (EoAD; dementia onset prior to age 65; $< 4\%$ of all AD), and are caused by mutations in presenilin-1 (PSEN-1), amyloid precursor protein (APP) or presenilin-2 (PSEN-2).[101] These gene products affect Aβ metabolism; FADAD mutations result in increased, relative, or absolute production of the $A\beta_{42}$. This strong link between all genetic determinants of AD and the overproduction of $A\beta_{42}$ has provided support for amyloid-related hypotheses and a majority of drug candidates tested in the last 15 or so years have posited an amyloid-related MOA.

Anti-amyloid DMTs

Antiamyloid DMTs have focused on three major MOAs: (1) reduction of $A\beta_{42}$ production (secretase inhibitors: gamma [γ]-secretase inhibitors, and β-secretase inhibitors); (2) reduction of Aβ-plaque burden via aggregation inhibitors; and (3) promotion of Aβ clearance via active or passive immunotherapy.

Reduction of $A\beta_{42}$ Production by γ-secretase Inhibitors/Modulators and β-Secretase Inhibitors

The $A\beta_{42}$ peptide is formed from the amyloid β-protein precursor (APP) by the sequential cutting actions of β- and γ-secretases. While reduction of $A\beta_{42}$ production by β- and γ-secretase inhibitors appeared as promising therapeutic approaches, and drugs in these classes have shown to reliably decrease $A\beta_{42}$ production in patients, concerns regarding adverse effects have slowed development of these drugs.

γ-Secretase inhibitors/modulators: the development of the γ-secretase inhibitor semagecestat was halted in phase III due to its association with worsening of daily function and increased rates of skin cancer and infections.[102] Development of avagecestat, another γ-secretase inhibitor, was halted in

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

phase II due to its association with higher progression rate from prodromal/MCI AD dementia, as well as increased rates of skin cancer.[103] Safety concerns for γ-secretase inhibitors stem from toxicity risks due to blocking of critical cell differentiation events related to interference with the NOTCH protein, a protein that plays an important role in control of normal cell differentiation and communication. Tarenflurbil (*r*-flurbiprofen, flurizan) was the first γ-secretase inhibitor stopped in Phase III due to lack of efficacy, and Tarenflurbil (Flurizan), the enantiomer of the non-steroidal anti-inflammatory drug flurbiprofen, a γ-secretase modulator, failed to show efficacy in a phase III program.

β-Secretase inhibitors: the development of *β*-secretase inhibitors (BACEi's), while still ongoing for some agents (elenbecestat, CNP520), has also recently encountered major difficulties that have resulted in discontinuation of several clinical trials, with agents in this class including verubecestat (MK-8931), atabecestat, lanabecestat, and LY3202606. A phase III verubecestat clinical program was discontinue due to futility in mild and moderate AD dementia, and treatment was associated with rash, falls and neuropsychiatric symptoms.[104] In a very recent late breaking news symposium at clinical trials AD (CTAD, Barcelona, October 24, 2018; available from: https://www.alzforum.org/print-series/1076786 for a report of the symposium) verubecstat, atabecestat, and LY3202626 were reported to be associated with detrimental effects on cognition in prodromal AD; atabecestat was also associated with liver toxicity. All agents show significant effects on reduction of $A\beta_{42}$ in the CSF, and while the mechanism causing relatively acute detrimental effects (mild to moderate effect sizes) on cognition for some of these agents is unknown, some posited suggestions include too much suppression, too quickly, of $A\beta_{42}$ production and levels, and off-target effects including BACE-2 inhibition.

Reduction of Aβ-plaque Burden via Aggregation Inhibitors

Agents with this MOA include ELND005 (scyllo-inositol), an oral $A\beta_{42}$ anti-aggregation agent. In preclinical studies, ELND005 slowed progression of AD pathology by neutralizing $A\beta_{42}$ oligomers, inhibiting toxic effects on synaptic transmission, preventing the formation and breaking down of $A\beta_{42}$ fibrils. A phase II study in mild and moderate AD did not show efficacy and suggested toxicity from higher doses tested (including death and infections).[105] Further development of the drug at the lowest dose (250 mg) has not progressed in the last several years.

Promotion of Aβ Clearance via Active or Passive Immunotherapy

Clinical trials in this MOA have dominated, and learnings from these negative trials have significantly impacted the AD drug development landscape in the past 15 years. Active immunotherapy with AN-1792, in the first human vaccination trial in AD, was discontinued in 2002 due to T cell-activated meningoencephalitis in 6% of vaccinated patients.[106] Consequently, the field turned to the development of passive immunotherapy approaches that would not risk T cell-mediated responses–the first agent of this class, bapineuzumab, did not show efficacy in two phase III clinical trials in mild and moderate AD.[107] However, valuable experience gained from several negative phase III bapineuzumab and solanezumab trials[108] paved the way for great insights regarding the need for requiring biomarker evidence of AD pathology, specifically "amyloid positivity," for subject inclusion in antiamyloid drug trials, the characteristics and association of amyloid related imaging abnormalities (ARIA) with antibody dose and Apolipoprotein ε-4 (Apoε4) genotype, necessity for higher dosing and evidence for target engagement (e.g., reduction of plaque burden on amyloid PET), low likelihood of treatment efficacy in dementia stages of AD, and the subsequent development and testing of multiple anti-Aβ "mabs" with different characteristics.

Passive Aβ immunotherapy: this amyloid-related MOA has been the most active and remains highly promising with several ongoing drug programs in phase III development, including aducanumab, gantenerumab, and BAN2401 in prodromal or very mild AD, and crenezumab, gantenerumab, and solanezumab in prevention trials for preclinical or at-genetic-risk populations.[92] Safety considerations related to this MOA include risk of ARIA. Phase I-b results from aducanumab suggested, for the first time, a congruent signal for the association of treatment-related reduction in cerebral amyloid burden and mitigation of clinical decline in patients with prodromal AD or very mild AD dementia.[109]

Active Aβ immunotherapy. following AN-1792, second generation anti-Aβ active immunotherapy agents were designed with higher specificity to Aβ sites to avoid T-cell activation. Second generation vaccines remain under development and include ACC-001 (underwent phase II testing),[110] CAD106[111] (under testing in the Alzheimer's prevention initiative, API), Generation 1 prevention trial in nonsymptomatic individuals who are homozygous for ApoE4), and Lu AF20513[112] (under Phase II testing in Stage two-third preclinical and prodromal AD).

Anti-Tau DMTs

Prevention of tau-Protein Phosphorylation or Fibrillarization, and Promotion of Clearance

The other major potential DMT MOA, and one that has not yet had agents advance to phase III development, is via anti-phospho-tau approaches. Potential approaches to prevent tau-phosphorylation and fibrillarization include glycogen synthetase kinase-3 (GSK-3) inhibitors (e.g., tideglusib–did not meet phase II endpoints), *τ* assembly inhibitors and aggregation inhibitors (e.g., methylene blue[113] and its derivative TRx0237), and microtubule stabilizers (e.g., davunetide–did not meet week 12 phase II endpoint), while those promoting clearance include anti-tau passive immunotherapy (ABBV–8E12, AADVac-1; BIIB092 in phase II testing).

Other MOAs and Symptomatic Agents

Cummings et al[92] provides a list of 40 putatively symptomatic agents in clinical trials for AD. The list includes agents with diverse MOAs, including sigma receptor agonists (AVP-786; AXS-05), SSRI's (escitalopram for agitation in AD);

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

cannabinoid receptor agent (nabilone), 5HT-6 antagonists (SUVN-502 in phase II testing as triple add-on to background ChEI and memantine combination therapy in mild and moderate AD; this MOA was not observed to be efficacious in phase III testing as add-on to background ChEI treatment[114]), PKC-modulators (bryostatin-1), glutamate receptor antagonists (riluzole), anti-epileptics (levetiracetam), and many others.

Insights from dozens of large and varied clinical trial programs in the last decade have provided cornerstones of ongoing intensive research efforts that aim to develop more accurate diagnostic tools (e.g., utilizing neuroimaging, blood, CSF, proteomic, and genomic biomarkers of AD) and better therapeutics via symptomatic and disease-modifying treatments for AD. Primary and secondary AD prevention trials are also underway. Multifactorial lifestyle intervention clinical trials (e.g., FINGER study [Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability][115]) and risk reduction of modifiable risk factors (see ►**Table 1**) also presents great opportunities to reduce the risk of AD and dementia.[1]

Summary

The current AD treatment paradigm is to mitigate symptoms and reduce clinical progression. Nonpharmacologic management and pharmacologic therapies, including FDA-approved AD medications (ChEIs and memantine), are aimed to minimize the disabling effects from cognitive and functional decline, and BPSD.

Clinicians should establish a proactive and flexible patient/dyad-centered approach to compassionately care for individuals with AD and their caregivers. Establishing and maintaining a strong therapeutic alliance that is holistic, pragmatic, and involves psychoeducation, behavioral and environmental strategies, appropriate pharmacotherapy, planning for current and future care needs, and promotion of brain health, and patient–caregiver dyad psychosocial well-being is central to competent and ethical care in AD.

Intensive research efforts remain underway to develop more accurate diagnostic tools and better AD therapeutics. A myriad of ongoing phase I–III human clinical trials for primary and secondary prevention, as well as symptomatic and disease-modifying treatment, are directed at diverse therapeutic targets in AD including neurochemicals, amyloid, and tau-pathological processes, mitochondria, inflammatory pathways, and neuroglia.

Financial Disclosures

Dr. Atri has no equity, shares, or salary from any pharma company and is not a member of any pharma speakers' bureau. He has received honoraria for consulting, educational lectures/programs/materials or advisory boards from AbbVie, Allergan, Alzheimer's Association, Biogen, Eisai, Grifols, Harvard Medical School Graduate Continuing Education, Lundbeck, Merck, Oxford University Press (medical book-related revenues), Sunovion, Suven, and Synexus. Dr. Atri's institution (Banner Health) has investigational observational study/trial related funding from Novartis. Dr. Atri's previous institution (California Pacific Medical Center) had contracts or received investigational clinical trial related funding from The American College of Radiology, AbbVie, Avid, Biogen, Lilly, Lundbeck, Merck, and vTV.

Conflict of Interest

None.

Acknowledgment

Dr. Atri is supported for this work by the Sun Health Foundation endowment at Banner Sun Health Research Institute, and by Banner Health.

References

1 Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet 2017;390(10113):2673–2734
2 Jack CR Jr., Bennett DA, Blennow K, et al; Contributors. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14(04):535–562
3 Tricco AC, Ashoor HM, Soobiah C, et al. Comparative effectiveness and safety of cognitive enhancers for treating Alzheimer's disease: systematic review and network metaanalysis. J Am Geriatr Soc 2018;66(01):170–178
4 Okura T, Plassman BL, Steffens DC, Llewellyn DJ, Potter GG, Langa KM. Neuropsychiatric symptoms and the risk of institutionalization and death: the aging, demographics, and memory study. J Am Geriatr Soc 2011;59(03):473–481
5 Kales HC, Chen P, Blow FC, Welsh DE, Mellow AM. Rates of clinical depression diagnosis, functional impairment, and nursing home placement in coexisting dementia and depression. Am J Geriatr Psychiatry 2005;13(06):441–449
6 Bhalerao S, Seyfried LS, Kim HM, Chiang C, Kavanagh J, Kales HC. Mortality risk with the use of atypical antipsychotics in later-life bipolar disorder. J Geriatr Psychiatry Neurol 2012;25(01):29–36
7 NICE: National Institute for health and Care Excellence. Dementia: assessment, management and support for people living with dementia and their carers. 2018. Available from: https://www.nice.org.uk/guidance/ng97; accessed January, 02, 2019
8 Ballard C, Corbett A, Howard R. Prescription of antipsychotics in people with dementia. Br J Psychiatry 2014;205(01):4–5
9 Weycker D, Taneja C, Edelsberg J, et al. Cost-effectiveness of memantine in moderate-to-severe Alzheimer's disease patients receiving donepezil. Curr Med Res Opin 2007;23(05):1187–1197
10 Cappell J, Herrmann N, Cornish S, Lanctôt KL. The pharmacoeconomics of cognitive enhancers in moderate to severe Alzheimer's disease. CNS Drugs 2010;24(11):909–927
11 Getsios D, Blume S, Ishak KJ, Maclaine G, Hernández L. An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom. Alzheimers Dement 2012;8(01):22–30
12 Getsios D, Blume S, Ishak KJ, Maclaine GD. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation. Pharmacoeconomics 2010;28(05):411–427
13 American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012;60(04):616–631
14 Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med 2008;168(05):508–513
15 Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK. The interface between delirium and dementia in elderly adults. Lancet Neurol 2015;14(08):823–832
16 Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in older persons: advances in diagnosis and treatment. JAMA 2017;318(12):1161–1174

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

17 Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ 2015; 350:h369
18 Schmidt R, Hofer E, Bouwman FH, et al. EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease. Eur J Neurol 2015;22 (06):889–898
19 Gauthier S, Patterson C, Chertkow H, et al. Recommendations of the 4th Canadian consensus conference on the diagnosis and treatment of dementia (CCCDTD4). Can Geriatr J 2012;15(04): 120–126
20 Atri A, Molinuevo JL, Lemming O, Wirth Y, Pulte I, Wilkinson D. Memantine in patients with Alzheimer's disease receiving donepezil: new analyses of efficacy and safety for combination therapy. Alzheimers Res Ther 2013;5(01):6–16
21 Rountree SD, Atri A, Lopez OL, Doody RS. Effectiveness of antidementia drugs in delaying Alzheimer disease progression. Alzheimers Dement 2013;9(03):338–345
22 Livingston G, Katona C. The place of memantine in the treatment of Alzheimer's disease: a number needed to treat analysis. Int J Geriatr Psychiatry 2004;19(10):919–925
23 Bullock R. Efficacy and safety of memantine in moderate-to-severe Alzheimer disease: the evidence to date. Alzheimer Dis Assoc Disord 2006;20(01):23–29
24 Atri A. Effective pharmacological management of Alzheimer's disease. Am J Manag Care 2011;17(Suppl 13):S346–S355
25 Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The galantamine U.S.A.-1 study group. Neurology 2000;54(12):2261–2268
26 Courtney C, Farrell D, Gray R, et al; AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004; 363(9427):2105–2115
27 Doody RS, Geldmacher DS, Gordon B, Perdomo CA, Pratt RD; Donepezil Study Group. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. Arch Neurol 2001;58(03):427–433
28 Farlow M, Anand R, Messina J Jr, Hartman R, Veach J. A 52-week study of the efficacy of rivastigmine in patients with mild to moderately severe Alzheimer's disease. Eur Neurol 2000;44(04):236–241
29 Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med 2012;366(10):893–903
30 Howard R, McShane R, Lindesay J, et al. Nursing home placement in the donepezil and memantine in moderate to severe Alzheimer's disease (DOMINO-AD) trial: secondary and post-hoc analyses. Lancet Neurol 2015;14(12):1171–1181
31 Tayeb HO, Yang HD, Price BH, Tarazi FI. Pharmacotherapies for Alzheimer's disease: beyond cholinesterase inhibitors. Pharmacol Ther 2012;134(01):8–25
32 Cummings JL. Alzheimer's disease. N Engl J Med 2004;351(01): 56–67
33 Cummings JL, Schneider L, Tariot PN, Kershaw PR, Yuan W. Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. Am J Psychiatry 2004;161(03):532–538
34 Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med 2008;148(05):379–397
35 Farlow MR, Cummings JL. Effective pharmacologic management of Alzheimer's disease. Am J Med 2007;120(05):388–397
36 Atri A, Rountree SD, Lopez OL, Doody RS. Validity, significance, strengths, limitations, and evidentiary value of real-world clinical data for combination therapy in Alzheimer's disease: comparison of efficacy and effectiveness studies. Neurodegener Dis 2012;10(1-4):170–174
37 Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet 2011;377(9770):1019–1031
38 Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006;(01):CD005593
39 Greenberg SM, Tennis MK, Brown LB, et al. Donepezil therapy in clinical practice: a randomized crossover study. Arch Neurol 2000;57(01):94–99
40 van de Glind EM, van Enst WA, van Munster BC, et al. Pharmacological treatment of dementia: a scoping review of systematic reviews. Dement Geriatr Cogn Disord 2013;36(3, 4):211–228
41 Rockwood K. Size of the treatment effect on cognition of cholinesterase inhibition in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2004;75(05):677–685
42 Mohs RC, Doody RS, Morris JC, et al; "312" Study Group. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001;57(03):481–488
43 Cummings JL, McRae T, Zhang R; Donepezil-Sertraline Study Group. Effects of donepezil on neuropsychiatric symptoms in patients with dementia and severe behavioral disorders. Am J Geriatr Psychiatry 2006;14(07):605–612
44 Wilcock G, Howe I, Coles H, et al; GAL-GBR-2 Study Group. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. Drugs Aging 2003;20(10): 777–789
45 Bullock R, Bergman H, Touchon J, et al. Effect of age on response to rivastigmine or donepezil in patients with Alzheimer's disease. Curr Med Res Opin 2006;22(03):483–494
46 Burns A, Gauthier S, Perdomo C. Efficacy and safety of donepezil over 3 years: an open-label, multicentre study in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2007;22(08): 806–812
47 Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. Arch Neurol 2004;61(02): 252–256
48 Doody RS, Dunn JK, Clark CM, et al. Chronic donepezil treatment is associated with slowed cognitive decline in Alzheimer's disease. Dement Geriatr Cogn Disord 2001;12(04):295–300
49 Gillette-Guyonnet S, Andrieu S, Cortes F, et al. Outcome of Alzheimer's disease: potential impact of cholinesterase inhibitors. J Gerontol A Biol Sci Med Sci 2006;61(05):516–520
50 Wattmo C, Wallin ÅK, Londos E, Minthon L. Long-term outcome and prediction models of activities of daily living in Alzheimer disease with cholinesterase inhibitor treatment. Alzheimer Dis Assoc Disord 2011;25(01):63–72
51 Wallin AK, Andreasen N, Eriksson S, et al; Swedish Alzheimer Treatment Study Group. Donepezil in Alzheimer's disease: what to expect after 3 years of treatment in a routine clinical setting. Dement Geriatr Cogn Disord 2007;23(03):150–160
52 Wallin AK, Gustafson L, Sjögren M, Wattmo C, Minthon L. Five-year outcome of cholinergic treatment of Alzheimer's disease: early response predicts prolonged time until nursing home placement, but does not alter life expectancy. Dement Geriatr Cogn Disord 2004;18(02):197–206
53 Wallin AK, Wattmo C, Minthon L. Galantamine treatment in Alzheimer's disease: response and long-term outcome in a routine clinical setting. Neuropsychiatr Dis Treat 2011; 7:565–576
54 Petersen RC, Thomas RG, Grundman M, et al; Alzheimer's Disease Cooperative Study Group. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352 (23):2379–2388
55 Lu PH, Edland SD, Teng E, Tingus K, Petersen RC, Cummings JL; Alzheimer's Disease Cooperative Study Group. Donepezil delays progression to AD in MCI subjects with depressive symptoms. Neurology 2009;72(24):2115–2121
56 McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev 2006;(02):CD003154

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

57 Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-best study (benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry 1999;14(02):135–146
58 Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348(14):1333–1341
59 Doody R, Wirth Y, Schmitt F, Möbius HJ. Specific functional effects of memantine treatment in patients with moderate to severe Alzheimer's disease. Dement Geriatr Cogn Disord 2004; 18(02):227–232
60 Grossberg GT, Pejović V, Miller ML, Graham SM. Memantine therapy of behavioral symptoms in community-dwelling patients with moderate to severe Alzheimer's disease. Dement Geriatr Cogn Disord 2009;27(02):164–172
61 Schmitt FA, van Dyck CH, Wichems CH, Olin JT; Memantine MEM-MD-02 Study Group. Cognitive response to memantine in moderate to severe Alzheimer disease patients already receiving donepezil: an exploratory reanalysis. Alzheimer Dis Assoc Disord 2006;20(04):255–262
62 van Dyck CH, Tariot PN, Meyers B, Malca Resnick E; Memantine MEM-MD-01 Study Group. A 24-week randomized, controlled trial of memantine in patients with moderate-to-severe Alzheimer disease. Alzheimer Dis Assoc Disord 2007;21(02):136–143
63 Wilcock GK, Ballard CG, Cooper JA, Loft H. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. J Clin Psychiatry 2008; 69(03):341–348
64 Wilkinson D, Andersen HF. Analysis of the effect of memantine in reducing the worsening of clinical symptoms in patients with moderate to severe Alzheimer's disease. Dement Geriatr Cogn Disord 2007;24(02):138–145
65 Wimo A, Winblad B, Stöffler A, Wirth Y, Möbius HJ. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. Pharmacoeconomics 2003;21(05):327–340
66 Winblad B, Jones RW, Wirth Y, Stöffler A, Möbius HJ. Memantine in moderate to severe Alzheimer's disease: a meta-analysis of randomised clinical trials. Dement Geriatr Cogn Disord 2007;24(01):20–27
67 Puangthong U, Hsiung GY. Critical appraisal of the long-term impact of memantine in treatment of moderate to severe Alzheimer's disease. Neuropsychiatr Dis Treat 2009;5:553–561
68 Abbott BP, Abbott R, Adhikari R, et al; LIGO Scientific Collaboration. All-sky LIGO search for periodic gravitational waves in the early fifth-science-run data. Phys Rev Lett 2009;102(11):111102
69 Wilkinson D, Schindler R, Schwam E, et al. Effectiveness of donepezil in reducing clinical worsening in patients with mild-to-moderate alzheimer's disease. Dement Geriatr Cogn Disord 2009;28(03):244–251
70 Peskind ER, Potkin SG, Pomara N, et al. Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial. Am J Geriatr Psychiatry 2006;14(08):704–715
71 Bakchine S, Loft H. Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study. J Alzheimers Dis 2008;13(01):97–107
72 Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT; Memantine MEM-MD-12 Study Group. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res 2008;5(01):83–89
73 Schneider LS, Dagerman KS, Higgins JP, McShane R. Lack of evidence for the efficacy of memantine in mild Alzheimer disease. Arch Neurol 2011;68(08):991–998
74 Schneider LS, Insel PS, Weiner MW; Alzheimer's Disease Neuroimaging Initiative. Treatment with cholinesterase inhibitors and memantine of patients in the Alzheimer's disease Neuroimaging Initiative. Arch Neurol 2011;68(01):58–66
75 Atri A, Shaughnessy LW, Locascio JJ, Growdon JH. Long-term course and effectiveness of combination therapy in Alzheimer disease. Alzheimer Dis Assoc Disord 2008;22(03):209–221
76 Rountree SD, Chan W, Pavlik VN, Darby EJ, Siddiqui S, Doody RS. Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease. Alzheimers Res Ther 2009;1(02):7
77 Chou YY, Leporé N, Avedissian C, et al; Alzheimer's Disease Neuroimaging Initiative. Mapping correlations between ventricular expansion and CSF amyloid and tau biomarkers in 240 subjects with Alzheimer's disease, mild cognitive impairment and elderly controls. Neuroimage 2009;46(02):394–410
78 Lopez OL, Becker JT, Whahed AS, et al. Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. J Neurol Neurosurg Psychiatry 2009 Jun; 80(06):600–607
79 Gillette-Guyonnet S, Andrieu S, Nourhashemi F, et al; REAL.FR study group. Long-term progression of Alzheimer's disease in patients under antidementia drugs. Alzheimers Dement 2011;7 (06):579–592
80 Vellas B, Hausner L, Frölich L, et al. Progression of Alzheimer disease in Europe: data from the European ICTUS study. Curr Alzheimer Res 2012;9(08):902–912
81 Patel L, Grossberg GT. Combination therapy for Alzheimer's disease. Drugs Aging 2011;28(07):539–546
82 Molinuevo JL. [Memantine: the value of combined therapy]. Rev Neurol 2011;52(02):95–100
83 Gauthier S, Molinuevo JL. Benefits of combined cholinesterase inhibitor and memantine treatment in moderate-severe Alzheimer's disease. Alzheimers Dement 2013;9(03):326–331
84 Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I; Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004;291(03):317–324
85 Choi SH, Park KW, Na DL, et al; Expect Study Group. Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate Alzheimer's disease: a multicenter, randomized, open-label, parallel-group study. Curr Med Res Opin 2011;27(07):1375–1383
86 Grossberg GT, Manes F, Allegri RF, et al. The safety, tolerability, and efficacy of once-daily memantine (28 mg): a multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors. CNS Drugs 2013;27(06):469–478
87 Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's disease cooperative study. N Engl J Med 1997;336(17):1216–1222
88 Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. JAMA 2014;311(01):33–44
89 Shah RC, Kamphuis PJ, Leurgans S, et al. The s-connect study: results from a randomized, controlled trial of Souvenaid in mild-to-moderate Alzheimer's disease. Alzheimers Res Ther 2013;5(06):59
90 Wattmo C, Wallin AK, Londos E, Minthon L. Predictors of long-term cognitive outcome in Alzheimer's disease. Alzheimers Res Ther 2011;3(04):23
91 van der Steen JT, Radbruch L, Hertogh CM, et al; European Association for Palliative Care (EAPC). White paper defining optimal palliative care in older people with dementia: a Delphi study and recommendations from the European Association for Palliative Care. Palliat Med 2014;28(03):197–209
92 Cummings J, Lee G, Ritter A, Zhong K. Alzheimer's disease drug development pipeline: 2018. Alzheimers Dement (N Y) 2018; 4:195–214
93 Davies P. A very incomplete comprehensive theory of Alzheimer's disease. Ann N Y Acad Sci 2000;924:8–16

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

94 Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci 2011; 12(12):723–738
95 Hyman BT. Amyloid-dependent and amyloid-independent stages of Alzheimer disease. Arch Neurol 2011;68(08):1062–1064
96 Selkoe DJ, Abraham CR, Podlisny MB, Duffy LK. Isolation of low-molecular-weight proteins from amyloid plaque fibers in Alzheimer's disease. J Neurochem 1986;46(06):1820–1834
97 Haass C, Koo EH, Mellon A, Hung AY, Selkoe DJ. Targeting of cell-surface beta-amyloid precursor protein to lysosomes: alternative processing into amyloid-bearing fragments. Nature 1992; 357(6378):500–503
98 Selkoe DJ. Amyloid protein and Alzheimer's disease. Sci Am 1991;265(05):68–71, 74–76, 78
99 Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science 1992;256(5054):184–185
100 Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297(5580):353–356
101 Loy CT, Schofield PR, Turner AM, Kwok JB. Genetics of dementia. Lancet 2014;383(9919):828–840
102 Doody RS, Raman R, Farlow M, et al; Alzheimer's Disease Cooperative Study Steering Committee; Semagacestat Study Group. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. N Engl J Med 2013;369(04):341–350
103 Coric V, Salloway S, van Dyck CH, et al. Targeting prodromal Alzheimer disease with avagacestat: a randomized clinical trial. JAMA Neurol 2015;72(11):1324–1333
104 Egan MF, Kost J, Tariot PN, et al. Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease. N Engl J Med 2018; 378(18):1691–1703
105 Salloway S, Sperling R, Keren R, et al; ELND005-AD201 Investigators. A phase 2 randomized trial of ELND005, scyllo-inositol, in mild to moderate Alzheimer disease. Neurology 2011;77(13):1253–1262
106 Orgogozo JM, Gilman S, Dartigues JF, et al. Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. Neurology 2003;61(01):46–54
107 Salloway S, Sperling R, Fox NC, et al; Bapineuzumab 301 and 302 Clinical Trial Investigators. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370 (04):322–333
108 Doody RS, Thomas RG, Farlow M, et al; Alzheimer's Disease Cooperative Study Steering Committee; Solanezumab Study Group. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370(04):311–321
109 Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 2016;537 (7618):50–56
110 van Dyck CH, Sadowsky C, Le Prince Leterme G, et al. Vanutide Cridificar (ACC-001) and QS-21 Adjuvant in Individuals with Early Alzheimer's Disease: Amyloid Imaging Positron Emission Tomography and Safety Results from a Phase 2 Study. J Prev Alzheimers Dis 2016;3(02):75–84
111 Winblad B, Andreasen N, Minthon L, et al. Safety, tolerability, and antibody response of active Aβ immunotherapy with CAD106 in patients with Alzheimer's disease: randomised, double-blind, placebo-controlled, first-in-human study. Lancet Neurol 2012; 11(07):597–604
112 Davtyan H, Ghochikyan A, Petrushina I, et al. Immunogenicity, efficacy, safety, and mechanism of action of epitope vaccine (Lu AF20513) for Alzheimer's disease: prelude to a clinical trial. J Neurosci 2013;33(11):4923–4934
113 Wischik CM, Staff RT, Wischik DJ, et al. Tau aggregation inhibitor therapy: an exploratory phase 2 study in mild or moderate Alzheimer's disease. J Alzheimers Dis 2015;44(02):705–720
114 Atri A, Frölich L, Ballard C, et al. Effect of idalopirdine as adjunct to cholinesterase inhibitors on change in cognition in patients with Alzheimer's disease: three randomized clinical trials. JAMA 2018;319(02):130–142
115 Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 2015;385(9984):2255–2263

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.