Current and Future Treatments in Alzheimer’s Disease

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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 (Aβ42)-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
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-Beta42 (Aβ42), tau (τ), and phospho-tau (p-tau) proteins in cerebrospinal fluid (CSF), as well as Aβ42-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

Table 1 Risk factors for AD dementia

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

Abbreviations: AD, Alzheimer’s disease; ApoE, Apolipoprotein E.

<sup>a</sup>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.
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...
institutionalization, higher distress, worse quality of life, and greater health care utilization and costs.\textsuperscript{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.\textsuperscript{6,7} BPDS 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.\textsuperscript{4,5} Treatment of BPDS 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.\textsuperscript{5}

Structured BPDS 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 BPDS 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 BPDSs) should be identified, modified, and continually assessed. Nonpharmacologic interventions and behavioral strategies against BPDS 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.

BPDS psychoeducation for caregivers should include some explanation of general models of the biopsychosocial substrates of BPDS 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 BPDS. 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.\textsuperscript{2–12}

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’ criteria)\textsuperscript{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\textsuperscript{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\textsubscript{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\textsubscript{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 BPDS, 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.\textsuperscript{5,17} 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.\textsuperscript{5,17} 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, caution 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,
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. The ChEIs and memantine have complementary mechanisms of action, potentially additive effects, and demonstrate acceptable tolerability and safety profiles. 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. 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.

The NNT to achieve significant 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. 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. 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.

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 pharmaco therapeutic 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 ChEIs 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 ChEIs: donepezil, rivastigmine, rivastigmine transdermal patch, galantamine, and galantamine extended-release

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (h)</th>
<th>Tmax (h)</th>
<th>Hepatic metabolism</th>
<th>Absorption affected by food</th>
<th>Reversible inhibition of AChE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>60–90</td>
<td>3–5</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>1.5–2</td>
<td>0.8–1.8</td>
<td>No</td>
<td>Yes</td>
<td>No*b</td>
</tr>
<tr>
<td>Rivastigmine Patch</td>
<td>3.4*a</td>
<td>8–12</td>
<td>No</td>
<td>No</td>
<td>No*b</td>
</tr>
<tr>
<td>Galantamine</td>
<td>5–8</td>
<td>0.5–1.5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Galantamine ER</td>
<td>25–35</td>
<td>4.5–5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: AChE, acetylcholinesterase; AD, Alzheimer’s disease; BuChE, butyrylcholinesterase inhibitor; ChEI, cholinesterase-inhibitors; Galantamine ER, galantamine extended-release capsules; Tmax, time to maximum plasma concentration.

*aRivastigmine has plasma half-life of 2–3.4 hours but a duration of action for AChE inactivation of 9 hours.

*bRivastigmine is a “pseudo-irreversible” inhibitor of AChE and BuChE.
ChEIs safety and tolerability: with slow titration in appropriate individuals, ChEIs are generally tolerated well and have an acceptable adverse effect profile. 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 ChEIs 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 exacerbated 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 daily living, and global status, and in ameliorating BPSD and caregiver burden. In the few studies that have directly compared ChEIs to each other, no significant differences were found. Longer term benefits of 2 to 4 years or more are also supported by longer term open-label extension and long-term prospective observational clinical cohort studies. Memantine XR 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (h)</th>
<th>T_{\text{max}} (h)</th>
<th>Hepatic Metabolism</th>
<th>Renal Excretion</th>
<th>Absorption Affected by Food</th>
<th>Other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memantine</td>
<td>60–80</td>
<td>9–12</td>
<td>Little (&lt; 10%)(^a)</td>
<td>Yes(^b)</td>
<td>No</td>
<td>10 mg twice daily max dose (20 mg total daily max)(^d)</td>
</tr>
<tr>
<td>Memantine XR</td>
<td>60–80</td>
<td>18–25(^c)</td>
<td>Little (&lt; 10%)(^a)</td>
<td>Yes(^b)</td>
<td>Yes(^c)</td>
<td>28 mg once daily max dose(^d)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; Memantine XR, memantine extended-release capsules; NMDA, N-methyl-D-aspartate; T_{\text{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_{\text{max}}) and 33% higher area under the plasma concentration–time curve from time 0 to 24 hour (AUC0–24))

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, those with depression or depressive symptoms). 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.
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.9,20,22,23,29,36–67 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.22,66,68,69

**Table 5** Comparison of adverse events (AEs) with an incidence ≥ 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 donepezil20

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

Abbreviations: AD, Alzheimer’s disease; APT, all-patients-treated; AE, adverse event; MMSE, mini-mental state examination. Data are number (%).

*Moderate to severe AD (MMSE 5–19 at baseline), receiving donepezil (10 mg/day).

bModerate AD (MMSE 10–19 at baseline), receiving donepezil (10 mg/d).

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.

**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...
Several months without adverse effects \(\text{initiated once patients have received stable ChEI therapy for patients with moderate to severe AD, memantine can be}

latter may be a particularly useful strategy in patients who

after several months of stable memantine monotherapy. The

...therapies, 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 cholinomimetic 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.\(^{30,53,75,76,90}\)

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>
<thead>
<tr>
<th>Drug</th>
<th>Dose and notes</th>
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</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>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.</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>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.</td>
</tr>
<tr>
<td>Galantamine</td>
<td>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.</td>
</tr>
<tr>
<td>Memantine</td>
<td>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.</td>
</tr>
<tr>
<td>Memantine XR/ donepezil capsule (branded combo capsule)</td>
<td>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.</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; ChEI, cholinesterase-inhibitors; FDA, Food and Drug Administration; NMDA, N-methyl-d-aspartate; Memantine XR, memantine extended-release capsules.
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investigational programs in the interim, the AD drug pipeline
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 development 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 Aβ42 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 intrasynthetically and interneuronally, thus leading to widespread cortical dysfunction. Other models have posited microvascular injury tipping the balance in favor of accumulation of toxic Aβ42 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 Aβ42. This strong link between all genetic determinants of AD and the overproduction of Aβ42 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 Aβ42 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 Aβ42 Production by γ-secretase Inhibitors/ Modulators and β-Secretase Inhibitors
The Aβ42 peptide is formed from the amyloid β-protein precursor (APP) by the sequential cutting actions of β- and γ-secretases. While reduction of Aβ42 production by β- and γ-secretase inhibitors appeared as promising therapeutic approaches, and drugs in these classes have shown to reliably decrease Aβ42 production in patients, concerns regarding adverse effects have slowed development of these drugs.

γ-Secretase inhibitors/modulators: the development of the γ-secretase inhibitor semagacestat 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
phase II due to its association with higher progression rate from prodromal/MCI AD dementia, as well as increased rates of skin cancer. 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 (β-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 (BACE1), 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. 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) verubecestat, 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 Aβ₄₂ 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 Aβ₄₂ 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 Aβ₄₂ anti-aggregation agent. In preclinical studies, ELND005 slowed progression of AD pathology by neutralizing Aβ₄₂ oligomers, inhibiting toxic effects on synaptic transmission, preventing the formation and breaking down of Aβ₄₂ 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). 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. 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. However, valuable experience gained from several negative phase III bapineuzumab and solanezumab trials 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 (ARIAs) with antibody dose and Apolipoprotein E-4 (ApoE4) 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. 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.

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), CAD106 (under testing in the Alzheimer’s prevention initiative, API). Generation 1 prevention trial in nonsymptomatic individuals who are homozygous for ApoE4, and Lu AF20513 (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., tidegulosa–did not meet phase II endpoints), and aggregation inhibitors (e.g., venetoclade–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 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);
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\(^{10}\), 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]\(^{15}\)) 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.

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**Conflict of Interest**

None.

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