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Alzheimer's Disease: Diagnosis, Treatment, and Future Outlook

First discovered by German psychiatrist and neurologist Alois Alzheimer in 1906, Alzheimer's disease (AD) is a chronic progressive neurodegenerative disease of the brain which causes memory loss, confusion, psychiatric disturbances, and disruption of daily life.[1] The pathological hallmarks of AD are amyloid beta (Aβ) plaque deposits and neurofibrillary tangles (NFTs) in the brain. AD is the most common dementia subtype, accounting for 50 -75% of dementia cases and ranked the 7th leading cause of death in the U.S..[2,3] Approximately 5.8 million people are affected by the disease in the U.S. with that number estimated to triple to 14 million by the year 2060.[4] During 2021, 4,562 Connecticut Medical Assistance Program patients received a diagnosis for AD, accounting for approximately 0.1% of the state's Medicaid population.

AD pathophysiology begins decades before the emergence of symptoms and diagnosis often occurs late in the course of illness when symptoms are overt, and the pathophysiological damage has been done. Genetic predisposition and environmental factors both contribute to AD. Lifestyle modifications such as daily exercise, healthy diet, control of chronic conditions (diabetes, hypertension, cardiovascular disease) can help prevent the emergence of AD in patients who are at risk.[1,5] Traditional treatment options for AD are palliative in nature and do not halt neuronal loss or improve cognitive function long term. More recent drug developments have focused on disease modifying therapies (DMTs) which remain controversial. AD affects all aspects of a patient's life including cognition, executive function, communication, social interaction, employment and career, independent living, emotional wellbeing, and self-perception.[6] Caregivers of AD patients struggle in providing 24 hour care as they witness the devastating effects of this disease.

Table 1. Modifiable Risk Factors of Alzheimer's Disease[5,34]

- Hypertension
- Diabetes
- Obesity
- Air pollution
- Head injury
- Excessive alcohol consumption
- Smoking
- Low level of education
- Low level of cognitive activity/ stimulation
- Poor diet
- Physical inactivity
- Depression
- Isolation
- Hearing impairment

There are two types of AD: early onset Alzheimer's disease (EOAD) and late onset Alzheimer's disease (LOAD). EOAD occurs prior to 65 years of age, presents as a more aggressive form with shorter survival time compared to LOAD, and accounts for 5-10% of AD cases.[7] The vast majority of EOAD cases are familial, however, only about 15% of cases have the genetic mutation identified. Known mutations associated with EOAD include defects in presenilin 1 (PSEN1), presenilin 2 (PSEN2), and the amyloid precursor protein (APP), all of which are involved in the production of Aβ.[1,7,8] LOAD is the most common type of AD occurring in patients > 65 years of age and is thought to be caused by a combination of older age, lifestyle risk factors, and genetic mutations or risk alleles.[8] The four risk allele pathways identified are Aβ metabolism, cholesterol metabolism, endocytosis, and immune response.[8] Patients who carry the apolipoprotein Eϵ4 (APOϵ4) genotype have the highest genetic risk for LOAD.[8] While genetic risk factors are invariable, lifestyle factors can be modified to delay and prevent cognitive decline (Table 1).[1,5]

The pathophysiological hallmarks of AD are the formation of extracellular Aβ plaques and intracellular NFTs in the brain which ultimately lead to neuronal cell damage and death. Under normal circumstances, Aβ works to protect the body from infection, repair neuronal cells, regulate synapses, and maintain the blood brain barrier (BBB).[9] Aβ is produced when Amyloid Precursor Proteins (APP) are cut or cleaved by α, β, and γ secretase enzymes within the periphery and brain. APP is found in many cells including microglia, astrocytes, and neuronal cells in the brain and kidney, heart, liver, and muscle cells in the periphery. α secretase cleaves APP in the periphery whereas β (BACE-1) and γ secretase cleave APP in the CNS into smaller Aβ peptide fragments. $Aβ_{42}$ fragments are specifically known to be neurotoxic, forming the AD hallmark Aβ plaques.[6,10] Tau is a protein found in the brain which under normal circumstances stabilizes the microtubular cytoskeleton of neuronal cells.[6] The formation of NFTs are caused by the hyperphosphorylation of tau. Excessive amounts of Aβ within the AD brain are thought to contribute to the irreversible hyperphosphorylation of tau leading to protein misfolding, accumulation and formation of intracellular tau tangles and further neuronal damage.[6,10,11] The combination of older age, genetics, and lifestyle risk factors contribute to the increased production and reduced clearance of Aβ and formation of NFTs.[8] Alone, Aβ does not guarantee the development of AD, however, the presence of NFTs, neurodegeneration, and Aβ accumulation is the best pathologic indicator of disease.[5] Other pathological changes associated with AD include vascular damage, loss of neu-

ronal synapses, blood brain barrier disruption, brain atrophy, decreased uptake of glucose by the brain, microglial activation, and infiltration of inflammatory cytokines.[7,8]

Just as there are several theories on the pathophysiological mechanisms of AD, there are several diagnostic guidelines for AD including the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), the US National Institute on Aging Alzheimer's Association Classification (NIA-AA), and the International Working Group Classification (IWG).[12-17] While there are subtle differences between them, the NIA-AA and IWG agree that there are **3 distinct stages of AD:**[12-16]

- Stage 1: Asymptomatic preclinical disease
- Stage 2: Mild Cognitive Impairment (MCI) due to AD (prodromal AD)
- Stage 3: AD dementia

The NIA-AA diagnostic guideline for asymptomatic preclinical disease is intended for research purposes only and is not designed to support a clinical diagnosis at this stage of disease. Biomarkers that may be used for a research based diagnosis of asymptomatic preclinical AD include:[12]

- Low Cerebral Spinal Fluid (CSF) $A\beta_{42}$
- Positive PET amyloid imaging
- Elevated CSF tau (total tau (t-tau) and/or phosphorylated tau (p-tau))
- Decreased fluorodeoxyglucose 18F (FDG) uptake on PET scan
- Brain atrophy on MRI

Measuring $A\beta_{42}$, t-tau, and p-tau directly from the CSF via lumbar puncture is preferred over plasma as it is in direct contact with brain extracellular fluid. Tau PET scans are now believed to provide stronger evidence of AD progression and cognitive decline compared to Aβ measurements.[18] Other potentially useful biomarkers include CSF BACE-1, which may be elevated in early disease, CSF or plasma neurofilament light (NfL) which can reflect nonspecific neurodegenerative disease, and CSF neurogranin which can reflect AD specific neurodegeneration.[5] Biomarker measurements are considered surrogate markers and do not directly correlate with advancement of disease. These measurements are intended as diagnostic tools for research purposes only.[12] Additional research and standardization is needed to support the use of biomarkers when making a clinical diagnosis.

The NIA-AA diagnostic guideline for MCI due to AD includes two sets of criteria, one for research purposes and another for clinical use.[15] If CSF t-tau and p-tau are high and $A\beta_{42}$ is low, this is a good indication that AD pathophysiological changes are occurring and a researched based diagnosis can be made.[18] A clinical diagnosis of MCI due to AD can be made if there is:[5,15]

- A decline in cognition
- Impairment in one or more cognitive domains (memory, executive function, attention, language, and visuospatial skills)
- Maintenance of independence with no change in occupational or social function

Screening tools that can be used to assess cognition include the Mini-Mental Status Exam (MMSE), the Memory Impairment Screen (MIS), the Montreal Cognitive Assessment (MOCA), the Mini-Cog, and the Saint Louis University Mental Status (SLUMS) Exam.[5,19] Patients suffering from AD are predominantly diagnosed during this stage due to the emergence of mild-moderate symptoms often presenting as work related issues, disinterest in hobbies, forgetting appointments and important dates, trouble with finances, and neuropsychiatric symptoms (irritability, anxiety or depression).[5] It is important to note that symptoms do not have an impact on independent living during this stage. A loved one or caregiver may be able to report these early signs rather than a patient self-reporting due to a lack of insight into symptoms. When considering a diagnosis of MCI due to AD, it is important to rule out other etiologies including but not limited to vascular dementia, Parkinson's dementia, Lewy body dementia, and dementia related to substance abuse or mental health disorders.[5,15]

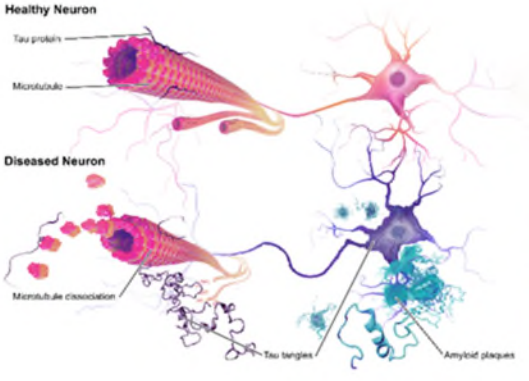
According to the NIA-AA guideline, AD dementia is the final stage. For diagnosis to occur, a patient must first be diagnosed with all cause dementia, meeting the following criteria:[16]

- Evidence of disruption in daily living (dressing, bathing, eating)
- Severe neuropsychological effects
- Impairment in two or more cognitive domains

Once diagnosed with all cause dementia, assessment and diagnosis of AD dementia can be made. Per the NIA-AA guideline, there are 3 categories of AD dementia:[16]

- Probable AD dementia – Patient meets criteria for all cause dementia. Patient has shown a gradual cognitive decline with a clear history of worsening cognition. There are clear cognitive deficits upon exam in which no other explanation exists (stroke, Lewy Body dementia, vascular dementia).
- Possible AD dementia - Patient meets criteria for all cause dementia but has sudden onset or lacks history of past cognitive symptoms or has evidence of a comorbid etiology (stroke, Lewy Body dementia, vascular dementia).
- Probable or possible AD dementia with evidence of the AD pathophysiologic process – Patient meets criteria for all cause dementia and for probable or possible AD dementia. Patient also displays evidence of AD biomarkers. This diagnosis is intended for research purposes only.

Traditional treatment options for AD are not curative and have only been shown to benefit symptoms of the disease for approximately 6 -18 months.[20,21] Acetylcholinesterase inhibi-



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tors (AChEIs) are considered first line therapy for AD and are FDA approved to treat mild-moderate disease. AChEIs inhibit the breakdown of acetylcholine (ACh), the neurotransmitter in the brain that helps to form and retrieve memories and retain focus and attention.[10] It is theorized that Aβ plaques in the brain lead to a loss of cholinergic neurons and weaken cholinergic transmission leading to memory dysfunction. By decreasing the breakdown of ACh, these medications improve cognition until continued loss of cholinergic neurons reaches a threshold where these medications are no longer effective.[11,20-21] Tacrine was the first FDA approved AChEI but was removed from the market in 2013 due to hepatotoxicity. There are currently three AChEIs on the market: donepezil, rivastigmine, and galantamine (Table 2). Donepezil is a highly selective, reversible AChEI formulated as an oral tablet and solution. In certain studies, donepezil showed improved cognition at higher doses but had greater incidence of side effects.[22] Rivastigmine is a partially selective, non-reversible AChEI and butyryl cholinesterase inhibitor formulated as an oral tablet and transdermal patch. Similar to the other drugs in this class, cholinergic adverse events are common and can include decreased appetite, nausea, vomiting, and diarrhea. Slow titration to maintenance dose or use of a transdermal dosing system can decrease incidence of adverse events.[22] Galantamine is a selective-competitive and reversible AChEI, and also modulates nicotinic receptors. Galantamine is formulated as an oral tablet, oral solution, and extended release capsule and carries the lowest risk of hepatotoxicity.[22] Although rare, AChEIs may enhance cardiac vagal tone resulting in bradycardia and AV block.[22]

The N-methyl D-aspartate (NMDA) receptor antagonist memantine (Table 2) is FDA approved for the treatment of moderate-severe AD. NMDA receptors are thought to be crucial for memory and cognition. Memantine is considered neuroprotective and works by binding uncompetitively to NMDA receptors in the brain thereby reducing excessive glutamate binding, which is thought to contribute to neuronal cell death in AD.[6] Memantine is formulated as both immediate and extended release oral tablets and has very few adverse effects with dizziness being the most important. In patients with moderate to severe AD, combination therapy with an AChEI and memantine is more beneficial than monotherapy. Extended release memantine and donepezil are available as a combination product. Although both AChEIs and memantine treat symptoms and improve cognition in the short term, they do not modify the disease or halt neuronal loss, and cognitive decline will continue in patients receiving these medications.[5]

DMTs (Disease Modifying Therapies) are intended to reduce, halt, or reverse the progression of a disease. Literature suggests that if DMTs are administered early enough in the course of AD, they may be able to slow or stop disease progression. Aducanumab (Table 2), an Aβ-directed monoclonal antibody, was approved by the FDA in 2021 for the treatment of MCI due to AD and AD dementia under accelerated approval contingent upon proving subsequent efficacy.[23] The two phase 3 trials for aducanumab, EMERGE (Efficacy and Safety of Aducanumab in Subjects with Early Alzheimer's Disease) and ENGAGE (Phase 3 Study of Aducanumab in Early Alzheimer's Disease) were initially terminated early based on futility analyses that predicted the studies would not meet the primary endpoint of improvement in cognitive decline. Although the studies were terminated early, data continued to be collected. While both trials were designed and executed almost identically, ENGAGE showed no improvement in the primary endpoint in both the low and high dose aducanumab groups, whereas EMERGE showed a statistically significant reduction in cognitive and functional decline in the high dose group.[24] Both trials met secondary endpoints of Aβ plaque reduction, and based on these surrogate reduction endpoints, this medication was approved by the FDA.[24] However, because of the inconsistent nature of EMERGE and ENGAGE coupled with the FDA's stipulatory accelerated approval, the scientific community is hesitant to trust the clinical efficacy of aducanumab. Additionally, CMS recently proposed a national coverage determination that only allows payment for aducanumab for Medicare patients who are enrolled in a qualifying clinical trial, sending a clear message that coverage is contingent upon trial enrollment that will likely prove or disprove efficacy.[25] Safety concerns discovered during EMERGE and ENGAGE included brain swelling and bleeding known as Amyloid Related Imaging Abnormalities (ARIAs). ARIA-E (edema) and ARIA-H (microhemorrhage) occurred in 41% of patients enrolled in clinical trials, 24% of which were symptomatic (headache, confusion, altered mental status, dizziness). ARIA is dose dependent, more likely to occur early in treatment, and MRI surveillance is recommended at baseline and prior to the 7th and 12th infusion.[26-28] Ultimately, significant concerns remain regarding aducanumab including safety and efficacy, duration of treatment, and administration and cost of the medication.

Despite the apprehension surrounding aducanumab, research and development of DMTs for AD is explosive. There are currently over 100 compounds in development, 50% of which are biologics.[6,29] Similar to aducanumab, many of the pipeline therapies target Aβ and while anti-amyloid therapies are effective at decreasing CSF and plasma Aβ, outcomes on halting disease progression and increasing cognitive function are lacking.[29,30] Other novel DMTs are designed to target tau, BACE-1 inhibition, apolipoprotein E, growth factors,

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and inflammatory mediators. However, preliminary outcomes for these are also lacking.[11,18,27,29,31] A better understanding of AD pathophysiology is needed to appreciate the role of biomarkers, targeted therapy, and when to initiate treatment. Treating mild-moderate AD after the brain has already developed Aβ plaques and NFTs may be too late to stop or reverse neuronal damage.[11]

While development of plaques and tangles is a normal aging process, excessive buildup leading to neuronal cell damage and death is the pathological definition of AD. These changes begin decades prior to the onset of symptoms making early detection and diagnosis paramount. Lifestyle choices such as daily exercise, eating healthy, and controlling chronic diseases have cognitive protective effects that can prevent the development of AD. Biomarkers, while helpful secondary measurements, do not always correlate with development of AD or a benefit on cognitive decline when targeted. As the field of AD advances, new medications must show a clinical benefit in slowing or halting the disease process and maintaining or increasing cognitive function.

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Table 2. Pharmacologic Treatments for Alzheimer's Disease

Drug	Dosing	Notable Side Effects	Caveats
Acetylcholinesterase Inhibitors (AChEIs)			
Donepezil (Aricept)	5 mg QD, titrating to a maintenance dose of 10 mg QD in moderate AD and 23 mg QD in severe AD	Nausea, vomiting, diarrhea, decreased appetite	Best tolerated of the AChEIs, administer in the evening If the 10 mg dose shows little or no benefit, consider the 23 mg dose which may be marginally better, but at the risk of more severe adverse GI effects
Rivastigmine (Exelon)	Patch: 4.6 mg/24 hours, titrating to a max of 13.3 mg/24 hours IR: 1.5 mg BID, titrating to a max of 6 mg BID	Nausea, vomiting, diarrhea, decreased appetite	Consider lower doses in hepatic and renal impairment and low body weight
Galantamine (Razadyne/ Razadyne ER)	IR: 4 mg BID, titrating to a maintenance dose of 8-12 mg BID ER: 8 mg QD, increasing to a maintenance dose of 16-24 mg QD	Nausea, vomiting, diarrhea, decreased appetite	Least tolerated of the AChEIs, administer in the morning with food, not recommended in severe hepatic impairment or ESRD, risk of bradycardia and AV block
NMDA Receptor Antagonists			
Memantine (Namenda)	IR: 5 mg QD, titrating to a maintenance dose of 10 mg BID ER: 7 mg QD, increasing to a maintenance dose of 28 mg QD	Headache, diarrhea, and dizziness	Use with caution with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) Drugs and clinical conditions (UTI), renal tubular acidosis) that raise urine pH decrease the elimination of memantine
Aβ Monoclonal Antibodies			
Aducanumab (Aduhelm)	IV Infusion (every 4 weeks) administered over one hour Infusion 1 and 2 - 1 mg/kg Infusion 3 and 4 - 3 mg/kg Infusion 5 and 6 - 6 mg/kg Infusion 7 and beyond 10 mg/kg	ARIAs	Clinical efficacy is controversial, more data is needed. Duration of treatment is not yet defined.

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