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Unraveling Alzheimer's: A holistic approach to diagnosis, stages and intervention

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder requiring a multifaceted approach to treatment and prevention. Pharmacological treatments provide symptomatic relief, with cholinesterase inhibitors (donepezil, rivastigmine, galantamine) enhancing cholinergic function and memantine regulating glutamate activity. Anti-amyloid monoclonal antibodies (aducanumab, lecanemab, donanemab) target amyloid plaques, potentially slowing cognitive decline but pose risks like amyloid-related imaging abnormalities (ARIA). Emerging therapies focus on tau-targeting strategies, including immunotherapies and small-molecule inhibitors, while advances in biomarkers such as tau-PET imaging and blood-based assays enhance early diagnosis. Preventive strategies emphasize lifestyle modifications, including regular exercise, cognitive engagement, and social interactions to support brain health. A Mediterranean diet rich in antioxidants and omega-3 fatty acids benefits cognition, while managing cardiovascular health, diabetes, and obesity reduces AD risk. Quality sleep, stress reduction, and mental well-being play essential roles, along with avoiding toxins, head injuries, smoking, and excessive alcohol. Early detection through genetic awareness and cognitive assessments enables timely intervention. Although no cure exists, integrating pharmacological and preventive measures enhances patient care, improves quality of life, and supports research toward disease-modifying treatments.

Keywords: Alzheimer's; Cholinesterase Inhibitors; Anti Amyloid Monoclonal Antibodies; Neuroimaging; Dementia

1. Introduction

Between 60 and 80 percent of dementia cases globally are caused by Alzheimer's disease (AD), a progressive neurological illness [1]. A reduction in cognitive abilities, such as memory, thinking, and the capacity to carry out daily tasks, is its defining feature. The cholinergic and amyloid hypotheses are the two main theories put forth to explain AD, which is thought to be a complex disease [2].

Amyloid-beta peptide buildup, which results in the development of neurofibrillary tangles and neurotic plaques in the brain, is a hallmark of AD. The medial temporal lobe and neocortical structures are the main targets of these pathogenic alterations, which cause brain cell loss [3].

Memory loss is the disease's primary symptom, but as it worsens, people may have a variety of serious cognitive and behavioural symptoms, such as paranoia, sadness, anxiety, rage, irritability, and insomnia [4]. As the disease advances, most individuals will require assistance with daily living activities.

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Age is the greatest risk factor for Alzheimer's disease (AD), with genetics also playing a role. Lifestyle and environmental factors, such as physical activity, education, and cardiovascular health, can influence the risk of developing AD **[**5].

The diagnosis of AD involves a combination of clinical assessments, cognitive testing, and imaging studies. In addition to providing endpoints for therapies intended to slow the progression of AD, cerebrospinal fluid and PET measurements of cerebral amyloidosis and tauopathy enable the diagnosis of AD even before dementia (prodromal stage) **[**6].

AD has no cure; treatment focuses on symptom management, slowing progression, and improving quality of life through support, lifestyle changes, and medications. Ongoing research aims to develop treatments, prevention strategies, and a deeper understanding of AD, with clinical trials and biomarkers advancing disease-modifying therapies **[**7]. AD poses challenges for individuals, families, and healthcare systems. Early detection and comprehensive care are key to effective management and better outcomes

2. Diagnosis of Alzheimer's Disease

Clinical assessment, neuroimaging, and biomarker testing are used to identify Alzheimer's disease, and new developments have improved early diagnosis.

2.1. Clinical Assessment

A psychiatrist, geriatrician, or neurologist evaluates cognitive decline by looking at the patient's medical history, the course of their symptoms, and how it affects their day-to-day activities. Medical history, medication use, and family history are evaluated to rule out other causes, while cognitive tests aid diagnosis. The MoCA detects early AD, while the MMSE screens for cognitive impairment. The Clock Drawing Test evaluates executive and visuospatial function, with neuropsychological testing providing a thorough assessment [8].

2.2. Physical & Neurological Examination

A physical and neurological exam assesses motor and sensory deficits to differentiate AD from other conditions and guide diagnosis and treatment.

2.3. Laboratory Tests: - To rule out other causes of cognitive decline:

Blood Tests: Lab tests help rule out reversible cognitive impairment, assessing autoimmune markers, infections, thyroid, liver, kidney, vitamin B12, and folate levels.

Genetic Testing: (In special cases) Genetic testing is considered for early-onset AD with a family history. PSEN1, PSEN2, and APP mutations indicate familial AD, while APOE ε4 is a risk factor. Genetic counselling is essential [9].

2.4. Neuroimaging Studies

Imaging helps identify AD-related brain changes and rule out other causes of dementia. Neuroimaging aids in the detection of AD-related brain alterations and the exclusion of other dementia causes. MRI and CT scans help diagnose AD by detecting brain abnormalities. MRI is preferred for identifying hippocampal shrinkage, while CT serves as a less detailed alternative [10]

Structural Imaging (Brain Anatomy): MRI detects hippocampal shrinkage and rules out other illnesses; CT is a less detailed alternative when MRI is unavailable.

Functional Imaging (Brain Activity): FDG-PET detects AD by assessing glucose metabolism, revealing reduced activity in temporoparietal regions due to neuronal dysfunction [11]. In certain situations, amyloid PET scans can help with research and accurate AD diagnosis by detecting amyloid plaques. By identifying tau tangles, tau PET imaging helps diagnose AD, distinguish it from other dementias, and plan an early intervention.

2.5. Cerebrospinal Fluid (CSF) Biomarkers

CSF biomarkers aid AD diagnosis by measuring elevated P-tau, increased T-tau, and decreased Aβ42 via lumbar puncture for early, accurate detection [12].

2.6. Emerging Biomarkers & Blood Tests

New blood biomarkers that have a good correlation with tau pathology, such as plasma p-tau217 and p-tau181, provide less invasive, highly specific options for early AD identification [13]. The plasma Aβ42/40 ratio indicates amyloid buildup, aiding early AD detection and enhancing screening, monitoring, and personalized care [14].

2.7. Differential Diagnosis (Ruling Out Other Causes)

Differentiating AD from other dementias is key to diagnosis and treatment. Vascular dementia shows stepwise decline with vascular damage on MRI. Lewy body dementia features parkinsonism, hallucinations, and fluctuating cognition. Frontotemporal dementia affects personality, while depression-related impairment may improve with therapy [15].

2.8. Diagnosis Staging

AD progresses in three stages. The preclinical phase shows no symptoms but has biomarker evidence. MCI causes mild cognitive issues while maintaining independence. In Alzheimer's dementia, severe decline requires caregiver support. Staging aids diagnosis, treatment, and prognosis [16].

AD diagnosis requires a multidisciplinary approach using clinical evaluation, imaging, and biomarkers. No single test confirms AD, but advances in fluid biomarkers and neuroimaging improve early detection

3. Stages of Alzheimer's Disease

AD is a progressive neurological disease with three main stages or seven stages per Dr. Barry Reisberg's Global Deterioration Scale (GDS).

Three-Stage Model of AD Progression

3.1. Early-Stage Alzheimer's (Mild Cognitive Impairment - MCI)

Mild cognitive impairment (MCI) often precedes Alzheimer's, with early detection crucial for intervention **[**17, 18]. Cognitive decline stems from hippocampal atrophy, tau tangles, and amyloid plaques. Screening tools like MoCA and MMSE aid early diagnosis [19].

3.2. Middle-Stage Alzheimer's (Moderate Dementia)

Early identification is vital as symptoms may mimic aging. MMSE and MoCA aid detection, with MoCA being more sensitive for MCI and early AD.

- Brain Changes: Mid-stage AD worsens memory, judgment, and language due to hippocampal and frontal lobe atrophy, requiring increased monitoring [20].
- Common Challenge: Families often struggle with caregiving stress at this stage due to behavioural symptoms and wandering risk.

3.3. Late-Stage Alzheimer's (Severe Dementia)

Late-stage AD causes severe decline, loss of recognition, minimal communication, mobility issues, and total caregiver dependence [21].

- Brain Changes: Advanced Alzheimer's leads to cortical shrinkage, severely impairing cognition, motor skills, and independence, requiring full-time care [22].
- End of Life Considerations: Advanced Alzheimer's causes cortical and motor decline, impairing cognition, movement, and swallowing, requiring full-time care.

4. Seven-stage model (global deterioration scale - GDS)

For a more detailed breakdown, the GDS Scale divides AD into seven stages:

The Global Deterioration Scale (GDS), by Dr. Barry Reisberg, assesses cognitive decline in dementia, including Alzheimer's, through seven stages of impairment [23].

Dementia progresses through seven stages, from mild memory issues to total dependence. Early stages involve minor cognitive decline, while moderate stages require assistance. Severe stages bring personality changes, incontinence, and loss of communication, leading to organ failure.

4.1. Factors Affecting Disease Progression

AD progression is influenced by age, genetics, lifestyle, and health, with APOE ε4 and conditions like diabetes accelerating decline, while a healthy lifestyle may slow it [24]

4.2. Treatment of AD

4.2.1. Cholinesterase Inhibitors in Alzheimer's Disease (AD)

Cholinesterase inhibitors (ChEIs) manage AD symptoms by inhibiting acetylcholinesterase, increasing acetylcholine levels to support cognitive function

4.3. Mechanism of Action

In AD, cholinergic neuron degeneration lowers acetylcholine levels [25]. Cholinesterase inhibitors prevent its breakdown, increasing availability for cognitive function [26].

By preventing Ache degradation, ChEIs enhance cholinergic neurotransmission, which can temporarily improve cognitive functions in AD patients.

4.3.1. Commonly Prescribed Cholinesterase Inhibitors

- Donepezil: Donepezil treats mild to severe AD by increasing acetylcholine, with side effects like nausea, diarrhea, and insomnia [27].
- Rivastigmine: Rivastigmine treats mild to moderate AD and Parkinson's dementia by increasing acetylcholine, available orally or as a patch to reduce GI side effects [28]
- Galantamine: Galantamine treats mild to moderate AD by inhibiting acetylcholinesterase and modulating nicotinic receptors, enhancing cognition. Side effects include nausea, dizziness, and appetite loss [29].
- Efficacy: Cholinesterase inhibitors improve cognition, function, and behavior in mild to moderate AD but do not alter progression. Donepezil, galantamine, and rivastigmine offer similar benefits [30]. Rivastigmine improves cognition, function, and well-being in mild to moderate AD, with treatment response varying by age and cognitive status [31].
- Safety and Tolerability: ChEI side effects include GI issues, cramps, and insomnia, often manageable with dosage adjustments; monitoring for bradycardia and weight loss is essential [32]
- Side Effects and Risks: ChEIs may cause GI, neurological, and cardiac side effects, requiring monitoring and dose adjustments [33].
- Contraindications & Precautions: ChEIs require caution in bradycardia, ulcers, asthma, COPD, and seizures due to effects on heart rate, digestion, and bronchoconstriction [34].
- Drug Interactions: ChEIs may interact with anticholinergics (reducing effectiveness), beta-blockers (worsening bradycardia), and NSAIDs (increasing GI bleeding risk) [35].
- Recent Developments: As of 2023, 187 trials studied 141 Alzheimer's treatments, focusing on DMTs, anti-amyloid antibodies, neuroinflammation, and precision medicine [36]

4.4. NMDA receptor antagonists

NMDA receptor antagonists regulate glutamate, preventing neurotoxicity and aiding Alzheimer's, Parkinson's, epilepsy, and chronic pain.

4.4.1. Mechanism of Action of NMDA Receptor Antagonists

Glutamate regulates NMDA receptors for memory, but excess in Alzheimer's causes neurotoxicity; NMDA antagonists protect neurons by reducing Ca^{2+} influx [37].

- NMDA antagonists are classified by inhibition type: uncompetitive (blocks ion flow, e.g., memantine) [38], competitive (blocks glutamate binding, e.g., AP5) [39], and non-competitive (modulates activity, e.g., eliprodil) [40].
- Memantine (Namenda): Memantine, FDA-approved for moderate to severe Alzheimer's, blocks excess glutamate while preserving normal synaptic function [41].
- Combination Therapy: Memantine combined with ChEIs improves cognition and function in moderate to severe AD more than monotherapy [42].
- Clinical Evidence: Memantine monotherapy improves cognition, behavior, and function, while combining it with donepezil enhances overall Alzheimer's outcomes.

4.4.2. Side Effects and Risks

- Common Side Effects: Common NMDA antagonist side effects include dizziness, confusion, hallucinations, headaches, and fatigue [43].
- Serious Risks: Prolonged NMDA antagonist use may cause psychosis, cognitive impairment, addiction risk, and cardiovascular effects [44].

4.4.3. Future Directions in NMDA Antagonist Research

NMDA antagonists like memantine are studied with neurotrophic and anti-inflammatory drugs for enhanced Alzheimer's treatment, with genetic profiling aiding personalized therapy [45].

5. Combinational therapy

Here is a thorough rundown of AD combo therapy

- Cholinesterase Inhibitors + Memantine: Namzaric (donepezil + memantine) combines ChEIs and NMDA antagonism to enhance cognition, daily function, and behavior in moderate-to-severe AD [46].
- Cholinesterase Inhibitors + Anti-Inflammatory Agents: NSAIDs may lower AD risk, but clinical trials show mixed results; combining them with ChEIs shows potential, though benefits remain uncertain [47].
- Cholinesterase Inhibitors + Antioxidants: Antioxidants like vitamin E may offer modest AD benefits with ChEIs, but evidence is weak, and some trials show safety concerns and cognitive decline risks [48].

5.1. Anti amyloid monoclonal antibodies

Anti-amyloid mAbs target Aβ plaques, supporting the amyloid hypothesis and slowing AD, but require monitoring for risks like infusion reactions and ARIA [49].

Anti-amyloid mAbs reduce Aβ plaque burden and neurotoxicity by targeting monomers, oligomers, and fibrils, facilitating clearance and microglial phagocytosis

- Aducanumab: In June 2021, the FDA approved aducanumab (Aduhelm®) for early-stage AD to reduce amyloid plaques, but its cognitive benefits remain controversial.
- Lecanemab: Lecanemab (Leqembi), approved in 2023, targets amyloid-beta protofibrils, reducing brain amyloid and slowing cognitive decline by 27% in early-stage AD over 18 months [50].
- Donanemab: Donanemab, approved by the FDA in July 2024, targets pyroglutamate-modified Aβ to reduce plaques and slow cognitive decline in Alzheimer's.
- Efficacy: Donanemab slowed decline by 35% and lecanemab by 27% in Phase III trials, showing cognitive benefits in mild to moderate AD but requiring ARIA monitoring [51].

Safety Considerations: ARIA, a key side effect of anti-amyloid mAbs, may cause headaches, nausea, and confusion, requiring MRI monitoring, while safety, cost, and access remain challenges [52].

5.2. Other experimental treatments

- Tau targeting: Tau tangles drive neuronal dysfunction in Alzheimer's, making them a key target for disease-modifying therapies.
- Current Therapeutic Strategies:
  - Immunotherapies: Tau immunotherapies include active vaccines (AADvac1, ACI-35) stimulating antibodies and passive monoclonal antibodies (ABBV-8E12, BIIB092) targeting tau for removal [53].

- Antisense Oligonucleotides (ASOs): Tau-targeting ASOs (MAPTRx) block mRNA to reduce tau levels, showing promise in a Phase 1 trial for moderate AD [54].
- Small Molecule Inhibitors: LMTX targets tau aggregation to slow disease progression and has undergone clinical evaluation [55].
- Gene Silencing Approaches: Gene silencing strategies, like antisense oligonucleotides, show promise in reducing tau levels. BIIB080 has demonstrated tau reduction

5.2.1. Key Developments

- **Tau Positron Emission Tomography (Tau-PET) Imaging:** Tau-PET imaging detects tau accumulation for early AD diagnosis and staging, identifying abnormal deposits before cognitive decline [56].
- **Cerebrospinal Fluid (CSF) Biomarkers:** Elevated CSF total tau and P-tau signal tau pathology and AD risk, even preclinically. Research seeks to refine these markers for better diagnosis [57].
- **Blood-Based Biomarkers:** Blood tests measuring tau biomarkers, like plasma P-tau217, offer a less invasive, accessible AD screening method, showing promising diagnostic accuracy **[**58].
- Advanced Imaging Techniques: Advanced MRI probes targeting hyperphosphorylated tau show promise for early detection, potentially identifying pathology before symptoms appear.

5.3. Preventive measures of AD

Despite extensive research, there is currently no proven way to prevent Alzheimer's disease. Lifestyle changes can reduce Alzheimer's risk and delay onset by promoting brain health and preserving cognitive function. Key preventive measures are outlined below.

5.3.1. Physical Activity

Frequent Exercise: Regular cardiovascular exercise, such as swimming, cycling, walking, and aerobics, improves brain blood flow, supports neurogenesis, and promotes overall brain health, helping reduce Alzheimer's risk [59]. Physical exercise boosts brain-derived neurotrophic factor (BDNF) levels, enhancing neuron growth, survival, and plasticity, and may protect existing neurons

5.3.2. Cognitive Engagement

- Mental Stimulation: Engaging in mentally stimulating activities, like reading, puzzles, or learning new skills, helps preserve cognitive function and prevent decline [60].
- Lifelong acquiring: Learning new skills and staying mentally active, through activities like classes, hobbies, or creative pursuits, can lower Alzheimer's risk [61].
- Social Interaction: Strong social connections and regular socialization can enhance cognitive health and reduce the risk of Alzheimer's by combating isolation and depression [62].

5.3.3. Healthy Diet and Nutrition

- Mediterranean Diet: Research suggests that a diet rich in fruits, vegetables, whole grains, lean meats, and healthy fats, especially omega-3s, supports brain function and reduces the risk of Alzheimer's, with the Mediterranean diet showing particular benefits [63].
- Antioxidants: Antioxidant-rich foods, including leafy greens, nuts, and berries, may reduce Alzheimer's risk, with flavonoids and vitamins E and C offering extra benefits [64].
- Omega-3 Fatty Acids: Omega-3 fatty acids in walnuts, flaxseeds, and fatty seafood may support brain health, but their role in preventing dementia remains unclear [65]. The risk of dementia rises with prolonged use of processed red meat [66].
- Limit Sugar and Processed Foods: A diet high in processed foods, trans fats, and refined sugars can increase insulin resistance and inflammation, raising Alzheimer's risk. Limiting these foods is recommended [67].

5.3.4. Cardiovascular Health

Managing blood pressure, cholesterol, diabetes, and weight through diet, exercise, and medication helps reduce Alzheimer's risk [68,69,70].

5.3.5. Sleep Health

Maintaining good sleep hygiene and treating sleep disorders can help reduce dementia risk and support brain health [71,72].

5.3.6. Mental and Emotional Health

Neuroticism increases Alzheimer's risk, while conscientiousness, openness, and agreeableness offer protection. Managing stress, anxiety, and depression through therapy, meditation, or mindfulness may help lower Alzheimer's risk and support brain health [73,74,75].

5.3.7. Social Engagement

Staying socially active helps lower Alzheimer's risk by preventing loneliness and cognitive decline [76].

5.3.8. Avoiding Toxins and Brain Injury

Prevent head injuries with helmets and fall prevention; quitting smoking and limiting alcohol reduce Alzheimer's risk [77].

5.3.9. Supplements and Other Therapies

Adequate vitamin D and certain supplements like antioxidants and omega-3s may support cognitive health, though more research is needed [78].

5.3.10. Genetics and Early Detection

Genetic testing and cognitive check-ups aid early Alzheimer's detection, while a brain-healthy lifestyle and risk management help reduce its risk [79,80].

5.3.11. Future Directions

Future directions in Alzheimer's disease (AD) treatment, management, and prevention are centred on improving early detection, developing more effective therapies, and focusing on holistic management strategies. Advancements in biomarker research, particularly blood-based tests, aim to identify AD in its earliest stages, enabling timely interventions [81]. Therapeutically, monoclonal antibodies targeting amyloid plaques, tau protein tangles, and neuroinflammation are showing promise in slowing disease progression. Additionally, repurposing drugs such as GLP-1 receptor agonists and exploring new molecular pathways offer potential breakthroughs. Personalized medicine, supported by AI-driven models, will allow for tailored treatment approaches. In terms of prevention, research emphasizes the importance of lifestyle interventions—such as maintaining cardiovascular health, engaging in regular physical activity, and promoting cognitive training—as essential strategies to reduce the risk or delay the onset of AD [82]. Furthermore, research published in *Signal Transduction and Targeted Therapy* emphasized the importance of targeting preclinical and mild cognitive impairment stages for early intervention, suggesting that managing modifiable risk factors could delay or prevent disease progression [83]. These studies collectively underscore the dynamic landscape of AD research, focusing on early detection, innovative treatments, and preventive strategies.

6. Conclusion

In conclusion, Alzheimer's disease remains a challenging and complex condition, with no cure currently available. However, advancements in diagnostics, pharmacological treatments, and non-pharmacological interventions are improving patient care and quality of life. Early detection, lifestyle modifications, and preventive strategies play crucial roles in managing the disease and reducing its risk. Ongoing research is vital for developing disease-modifying therapies, better diagnostic tools, and enhancing our understanding of the disease to provide better support for affected individuals and their families.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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