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Mapping the Future: Disease-Modifying Treatments for Alzheimer's

Patient selection criteria and clinically approved disease-modifying treatments

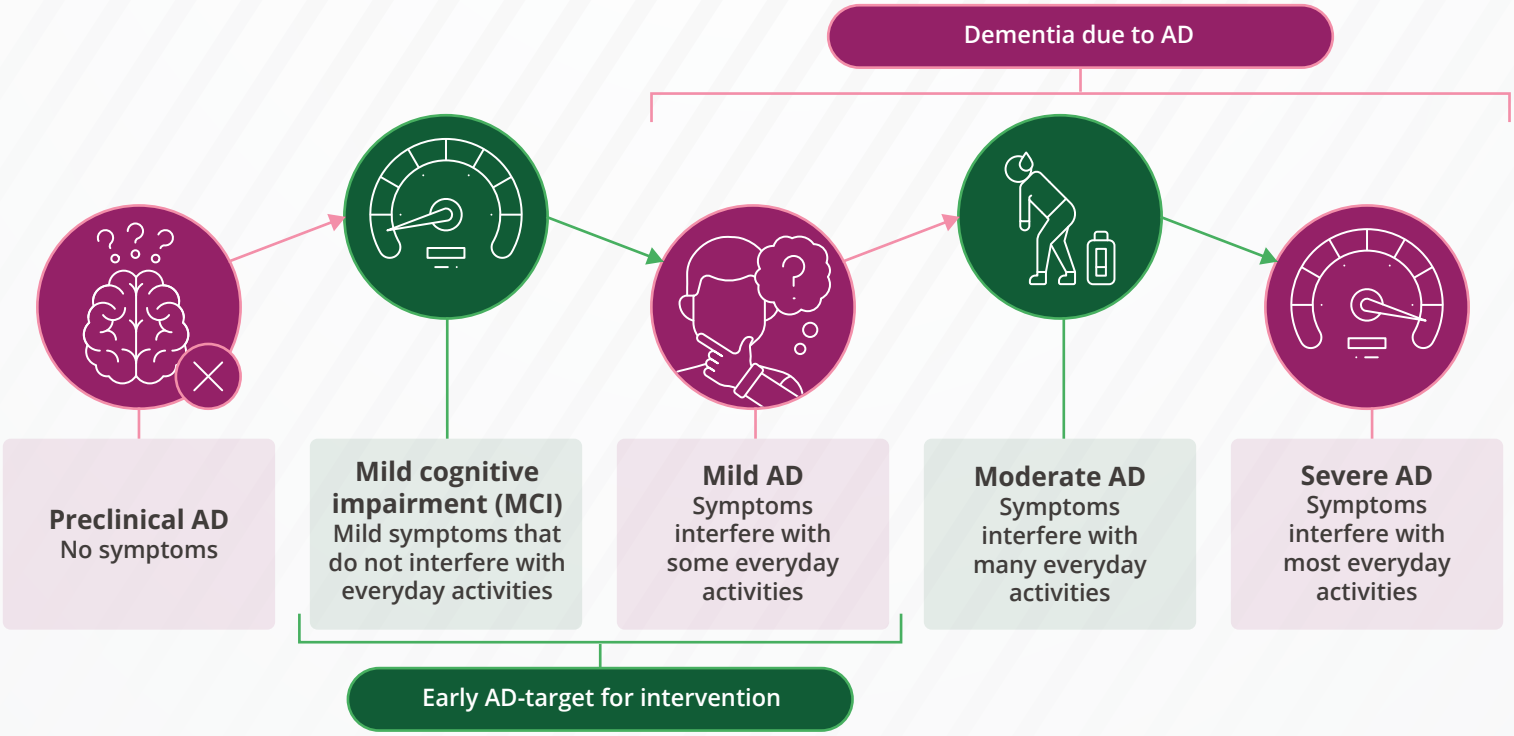
Overview of Alzheimer's disease (AD)

AD is a chronic progressive neurodegenerative disease and the most common cause of dementia in the elderly, accounting for 50–75% of all cases[1]

Population ageing → Increased life expectancy → Increased prevalence of dementia[1]

In the Asia-Pacific region, the number of people living with dementia is expected to increase from 23 million in 2015 to almost 71 million in 2050[1]

AD progression[1,2]



Treatment

Current pharmacological interventions[3,4,5]

- Cholinesterase inhibitors
  - Donepezil, rivastigmine, and galantamine (FDA approved)
- N-methyl-D-aspartate receptor antagonists
  - Memantine (FDA approved)
- Drugs targeting the brain-gut axis (gut microbiota)
  - Gastrodin (not approved yet)

- Provide symptomatic benefits
- Neither halt nor reverse disease progression

FDA: Food and Drug Administration

Newer advanced therapeutics tackling the root causes of AD offer hope for treatments that both relieve symptoms and slow disease progression, improving patient outcomes and quality of life[3]

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Disease-modifying therapies (DMTs) targeting the underlying pathophysiology of AD[1,3]

Amyloid-β (Aβ) accumulation forming plaques
• Anti-Aβ monoclonal antibodies help clear Aβ deposits

Hyperphosphorylated tau protein forming neurofibrillary tangles
• Tau-targeting therapies are awaiting validation

Synaptic plasticity/ neuroprotection

Neuroinflammation

Neuropsychiatric symptoms such as agitation associated with dementia due to AD

Aβ accumulation and hyperphosphorylated tau precede the AD symptoms by several years[6]

Monoclonal antibodies targeting Aβ proteins → Significant reduction in the rate of cognitive and functional decline in patients with early AD or MCI[1]

Anti-Aβ approved for clinical use

Lecanemab (Biogen/Eisai)
• Targets Aβ oligomers, fibrils, and plaques
• Clarity AD clinical trial
  - ↓ Clinical decline by 27% at 18 months compared to placebo
  - Most common adverse events: infusion reactions, combined cerebral microhaemorrhages and macrohaemorrhages, superficial siderosis, oedema/effusion, headache, and fall[7]
• High safety
• Approved in the United States, Japan, China, South Korea, Hong Kong, Israel, UAE, Great Britain, Mexico, and Macau[7]
• Received a positive opinion from the European Medicines Agency, recommending approval[7]

Donanemab (Eli Lilly)
• Targets Aβ plaques
• TRAILBLAZER-ALZ 2 Phase 3 study[8]
  - Slowed cognitive and functional decline by up to 35% compared to placebo at 18 months
  - ↓ Amyloid plaques on average by 61% at 6 months
• Moderate safety
• Approved in the United States, Japan, China, and Australia[9,10]

Aβ monoclonal antibodies in clinical trials[3]

Remternetug
• Targets Aβ with N-terminal Asp3 pyroglutamation (N3pG Aβ) antibodies
• Moderate safety

SHR-1707 (Hengrui Medicine)
• Targets Aβ fibrils and monomers, blocking the formation of Aβ plaques
• Received approval from the National Medical Products Administration for clinical trials in China

Amyloid-related imaging abnormalities (ARIA) are a side effect of anti-amyloid DMTs[6]

Increased rate of Aβ plaque clearance in close proximity to blood vessels causes damage and vascular permeability[1,3,11]

• Associated with oedema or haemorrhagic changes
• Transient and observed in magnetic resonance imaging (MRI)
• Very few are symptomatic with dizziness, headache, visual disturbances, and increased mental confusion
• Necessitates routine MRI monitoring

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Administration of DMTs targeting early AD necessitates a paradigm shift towards early detection, accurate diagnosis, and timely management of AD

Advanced biomarker-based diagnostic modalities[2]

Positron emission tomography (PET) imaging for Aβ deposits
- Highly sensitive and specific to AD

Biomarker concentration in cerebrospinal fluid (CSF)
- $A\beta_{42}$ or the $A\beta_{42}/A\beta_{40}$ ratio
- Phosphorylated tau (p-tau181) and total tau
- Neurofilament light chain

FDA approved blood biomarker pTau217/β-Amyloid 1-42 Plasma Ratio[12]

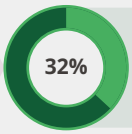
Patient selection criteria are essential to a wider distribution of anti-amyloid DMTs, as they are effective only at the early stages of AD[4]

Physical frailty as treatment is physiologically demanding[4]
- Frequent infusions
- Regular MRI monitoring

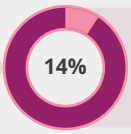
Genetic screening for apolipoprotein E ε4 (*APOE4*) alleles is essential[1,4]
- *APOE4* homozygotes are more likely to develop ARIA

Patients with MCI due to AD as confirmed by cognitive assessment tools and amyloid biomarker tests (amyloid- PET, tau in CSF)

Patients attending memory clinics/specialist cognitive services:



Considered for DMTs



Eligible for treatment

Institutional readiness for anti-amyloid therapies for early AD should include[1]:

Best practices for the identification and diagnosis of eligible patients
- Large-scale screening measures using imaging modalities that detect amyloid and tau pathology in the brain and biomarkers in CSF or blood
- Genetic testing for contraindications/eligibility

Safe administration of anti-amyloid monoclonal antibodies
- Standardised workflows and checklists
- Defined start and stop criteria

Monitoring of treatment
- Infusion centres and infrastructure with capacity to deliver anti-amyloid agents, emergency care facilities, administrative staff to schedule the infusions and follow-up with the patients
- Regular biomarker testing to monitor treatment response
- *APOE4* genetic testing to inform patient decisions regarding anti-amyloid therapy

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Institutional readiness for anti-amyloid therapies for early AD should include[1]:

Education
- Increase awareness and knowledge of early AD symptoms among primary care providers, family members, and the general public

Cross-disciplinary collaboration
- Clinicians, infusion nurses, neuroradiologists, geriatricians, and psychiatrists

Managing potential adverse events
- Infusion reactions and ARIA
  - Awareness about the potential for ARIA among patients and caregivers, trained neurologists, and established protocols to identify and manage ARIA, access to hospital beds and intensive care units

Key messages

- Anti-amyloid DMTs for early AD have revolutionised the care for patients with neurodegenerative diseases
- Novel biomarkers for non-invasive, high-throughput detection of pre-symptomatic AD would greatly improve the diagnostic capacity and are an unmet need
- Education and training will be the cornerstone for the establishment of new pathways of care for the identification of patients with early AD and delivery of DMTs in a safe and efficient manner
- Investment in registries, and collection and analysis of real-world long-term data through a learning healthcare system will greatly benefit the development and administration of future DMTs

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