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The Current Treatment Landscape of Alzheimer's Disease

Insights on emerging therapies, patient-centred approaches, and lifestyle interventions

Understanding clinically meaningful benefits of treatments for Alzheimer's disease (AD)[1,2]

Defining minimal clinically important difference (MCID)

MCID refers to the smallest difference in patient outcome of interest, indicating the need for modifications in the patient's management

Current approaches to calculating MCID have methodological limitations that affect their applicability

Differentiates between statistical significance and the clinical meaningfulness of treatment effects

The US Food and Drug Administration considers Clinical Dementia Rating–Sum of Boxes Score (CDR–SB) as evidence of treatment efficacy in early AD

MCID thresholds and alternatives[1]

Alternate approaches to evaluate the clinical benefits of AD therapies do not consider MCID and instead confer predictive and cumulative benefits

Predictive benefit
Amyloid plaque reduction can indicate potential clinical benefits in AD trials

Cumulative benefit
Refers to the accumulation of clinical benefits with extended duration of AD treatment

Time saved with treatment
Considers the clinical benefit of small differences in cognitive scale scores over time

Electroencephalography (EEG) abnormalities in AD[3]

Epileptiform discharges on EEG correlate with memory decline, behavioural changes, and clinical seizures in AD

Identifying these features aids in recognizing high-risk patients and personalising treatment

A three-step approach to evaluating the clinical benefits of AD therapies[1]

1. To establish if the change is clearly noticeable and can easily be communicated
2. To assess if the change is valuable and associated with improved function, quality of life, or disease stage
3. To ascertain if the change outweighs specific considerations like side effects, treatment costs, inconvenience, or required duration of time

This three-step approach can be adopted to evaluate the clinical benefits with respect to individuals, groups (patients, caregivers, and clinicians), and healthcare systems

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Monoclonal antibodies targeting amyloid β (mABs) in AD[2]

Treatment efficacy of mABs during clinical trials

- Achieved 60% to 85% reduction in amyloid β levels over 18 months
- Up to 80% of study participants were 'amyloid-negative' post mAB treatment

Clinical benefits of mAB treatment

- Evaluated using the CDR scale and the Integrated Alzheimer's Disease Rating Scale
- EMERGE trial demonstrated a 22% slowing of cognitive decline

Cognitive decline was slowed between 22% and 36%, depending on the treatment used

- mABs reduced CDR-SB decline by ~0.5 over 18 months, implying a slight impairment in a single domain

Adverse effects and tolerability associated with anti-amyloid β therapy

- Adverse effects include amyloid-related imaging abnormalities (ARIA) and infusion-related reactions
- Treatment discontinuation rates were low, ranging between 6.9% and 13.1%, depending on the treatment choice

Management of ARIA and infusion-related reactions

- Intracerebral oedema/effusion (ARIA-E) and haemorrhage (ARIA-H) were key ARIA risks
- ARIA-E was more frequent in study participants treated with mABs (12.6–34.8%) compared to placebo (1.7–2.1%)
- Treatment-related deaths due to serious ARIA: 0.4%
- <3.5% of ARIA cases required treatment cessation

Practical considerations and monitoring associated with mAB therapy

- Time commitments
- Fortnightly or monthly clinic visits for up to 18 months
- 1-hour intravenous infusion time in addition to pre- and post-infusion observation period

Assessments required for mAB eligibility

- Lumbar puncture or positron emission tomography scan to confirm high levels of Aβ
- *APOE* genotyping is recommended for prediction of ARIA risks
- A minimum of three brain magnetic resonance imaging (MRI) scans are recommended to detect and manage ARIA within the first year of treatment

The current scenario in Australia

Guidelines to evaluate patients for mAB treatment as well as administering therapy are not yet established

Limited real-world studies to identify the percentage of patients with mild cognitive impairment or early AD dementia who would be eligible for mAB therapy after the exclusion of patients with medical comorbidities

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Collaborative and equitable dementia care[2]

Multidisciplinary collaboration among general practitioners, specialists, nurses, allied health professionals, and the healthcare system is essential

Care models must address disparities between rural/regional and metropolitan clinics to ensure equitable access

Involvement of patients in clinical decision-making[2]

- Complex scientific terms such as relative risk and hazard ratios must be elucidated, as these can confuse the patient, carer, or family
- Simpler language, absolute risks, and graphics such as icon arrays must be used to explain trial data to patients
- Personalised assessment of the MCID construct can aid the evaluation of clinical benefits from trials

Key aspects to be addressed during individualised discussion of mAB therapy with the patient

- Patient's suitability to mAB therapy based on the inclusion and exclusion criteria of the clinical trial
- Testing and eligibility requirements, including associated treatment costs and time commitments
- Discussion of potential benefits of mAB therapy using functional and outcome changes with patient-specific scenarios
- Outline of clinical and imaging safety monitoring procedures, including associated financial and time costs
- Adverse effects of mABs and their implications on treatment continuation and overall health
- Patient-centred, shared decision-making process regarding the suitability of mAB therapy
- Role of multidisciplinary care team for patients, carers, and families

Incorporating digital medicine into AD management[4]

- Early detection through smartphone apps and web-based platforms enables quicker identification of potential AD cases
- Digital monitoring of physical activity, sleep patterns, and real-time tracking of vital signs to provide ongoing insights into AD progression and individual health
- Digital cognitive assessments that track disease progression by measuring cognitive functions regularly help to personalise treatment strategies

A proposed blueprint for diagnosis and care in the early stages of AD[5]

	Detection	Assessment	Diagnosis	Treatment and monitoring
Stage	Identifying individuals who may benefit from treatment for cognitive impairment	Evaluating individuals with cognitive impairment and excluding those with non-AD causes of cognitive impairment	Confirming AD pathology and determining treatment options	Providing treatment and monitoring AD disease progression
Healthcare providers (HCPs)	Non-dementia-trained HCPs	Dementia-trained HCPs	Dementia specialist	Dementia care team
Tests and diagnostic activities	• Population screening • Family history • Quick memory test • Memory complaint	• Quick memory test • Genetic test • In-depth memory test • Fluid biomarker	• Differential diagnosis • AD pathology • Communicating the diagnosis	• Initiating AD treatment • Monitoring MRI/vital signs and related adverse effects

Approaches to improve AD care[5]

Establishing awareness

- Raising awareness about AD and the benefits of early AD detection in the general population
- Education and research for identifying AD risk factors and collecting individual patient data
- Training non-dementia-focused HCPs to detect early AD and support the patient
- Training of HCPs to stratify patient risks and refer to dementia care team

Patient-centred support

- Creation of training programs or certifications for interested nurses
- Developing a patient resource toolbox
- Increasing access to services and information via web platforms and tools
- Creating volunteer groups to disseminate technical information

Building processes and capacity for integrated care teams

- Improving curriculum and training for future dementia-trained HCPs
- Developing a business case model to generate senior management support
- Enhancing communication flows within the clinic and with external stakeholders
- Integrating research components in the care model

Prevention potential of AD[6]

- The long period of progressive accumulation of brain pathology from asymptomatic stages to the onset of cognitive decline and dementia provides an opportunity for both early detection and prevention
- ~40% of all dementias can be attributed to modifiable lifestyle and environmental factors that can be prevented or managed
- The prevention potential of AD can be higher in low-middle income countries with increasing dementia burden

Risk factors of dementia[6]

- Diabetes
- Obesity at midlife
- Physical inactivity
- High blood pressure at midlife
- Depression
- Smoking
- Low education
- Hearing loss
- Traumatic brain injury
- Excessive consumption of alcohol
- Social isolation
- Air pollution
- Emerging risk factors like sleep disturbances, stress, poor oral health, and infections

Evidence-based interventions to reduce the risk of dementia[6]

- Physical activity interventions
- Tobacco cessation interventions
- Nutritional interventions
- Cognitive interventions
- Weight management
- Interventions for excessive alcohol use
- Management of hypertension
- Management of diabetes
- Management of lipid levels

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study model[6]

First large-scale randomized controlled trial (N = 1,260) involving multimodal lifestyle-based interventions that led to significant cognitive benefits in the at-risk, elderly population

- ~25% improvement in global cognition
- Risk of chronic diseases: ↓60%
- Risk of cardiovascular events: ↓20%
- Cost-effective, with substantial societal benefits

Biological mechanisms underlying multimodal interventions

Multimodal interventions may exert their effects on cognition via synergistic mechanisms by:

- Reducing vascular factors and pathways
- Modifying lipid homeostasis in brain tissue
- Increasing neurotrophic factors

Lifestyle intervention–pharmacological treatment combination

Multimodal precision prevention interventions
- Neuronal injuries, proteinopathies
- Vascular pathology
- Biology of aging in the brain
- Resilience

Tools to accurately assess at-risk populations
- Risk scores
- Blood biomarkers
- Digital screening tools
- Clinical phenotyping

Matched interventions for different bio-phenotypes
- FINGER lifestyle intervention
- FINGER + targeting inflammation
- FINGER + targeting glucose metabolism
- FINGER + targeting amyloid or proteinopathies
- FINGER + future mechanistic targets

Multimodal non-pharmacological interventions (MNPIs) for delaying cognitive decline[7]

- MNPIs are recommended as first-line therapy for behavioural and psychological symptoms of dementia
- MNPIs have the potential to address multiple modifiable risk factors contributing to cognitive decline
- The effectiveness of early MNPI in the elderly population with dementia has been established[5]
  - Significantly higher cognitive preservation in remote memory, orientation, drawing, and language

Dementia policies and healthcare system preparedness across countries[8]

Country	United States	Germany	Sweden	United Kingdom	China	Japan	Republic of Korea
Initiatives	National plan, public health initiatives, and research on early detection and risk reduction	Public health initiatives and research efforts	Research-focused early detection and risk reduction initiatives	National plan, public health initiatives, and early detection research	National plan, public health initiatives, and early detection research	National plan, public health initiatives, and early detection research	National plan, public health initiatives, early and regular brain health screening, and research efforts

Key messages

Insights into clinically meaningful benefits of AD therapy can inform HCPs, patients, and caregivers about treatment options and therapeutic efficacy while simultaneously considering treatment costs

Combining multimodal lifestyle interventions with disease-modifying drugs presents a novel precision prevention approach to address multiple risk factors and disease mechanisms simultaneously

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