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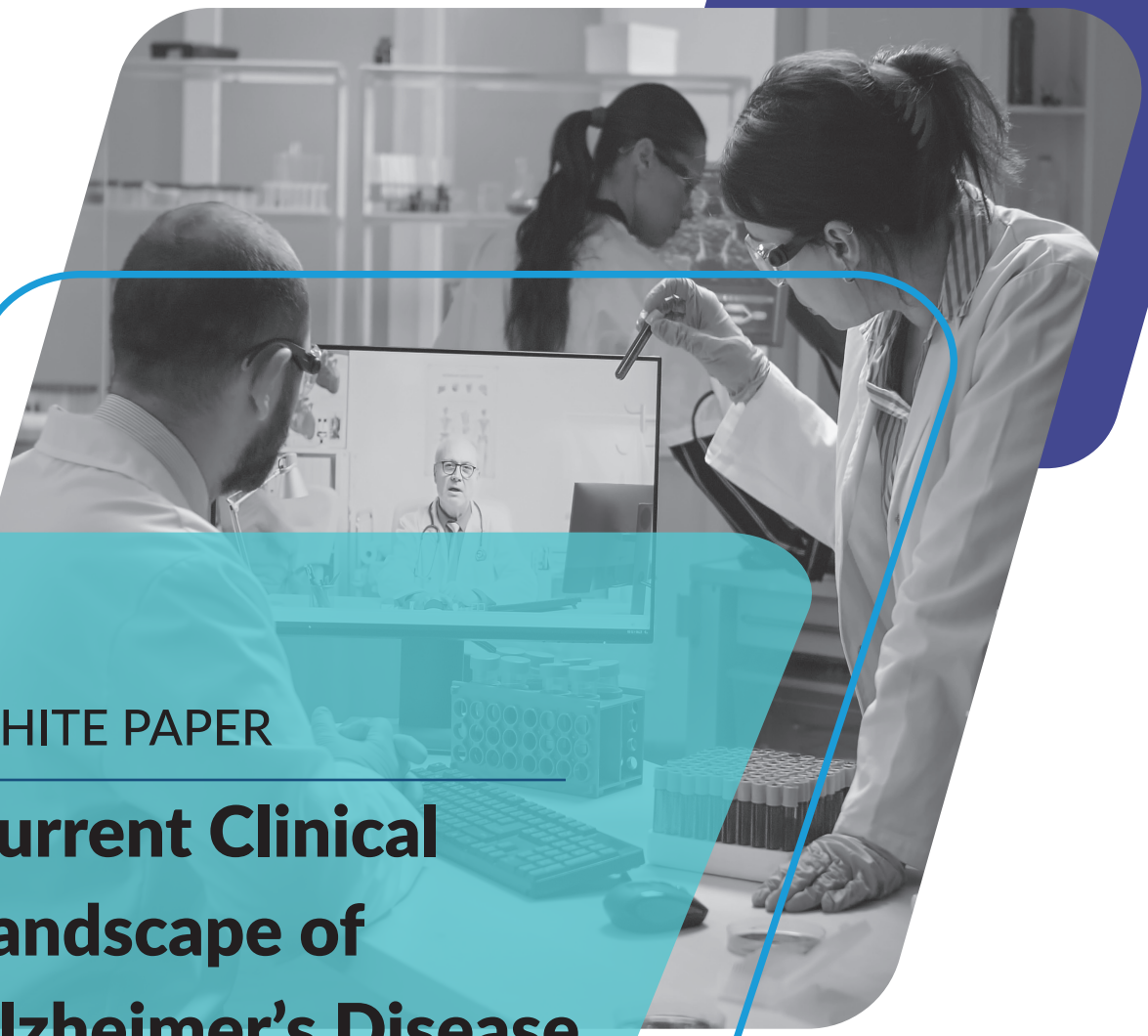

WHITE PAPER

Current Clinical Landscape of Alzheimer's Disease

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CONTENTS

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that impairs memory, language skills, behaviour and thinking. It is the most common form of dementia, and research in the past several decades has led to advancements in slowing down the deterioration of cognition in AD patients. While the exact cause of AD remains uncertain, researchers believe that the accumulation of proteins, such as β-amyloid (Aβ) and τ-protein, as well as reduced levels of neurotransmitters i.e., acetylcholine (ACh) play a crucial role. Pursuing effective AD treatments involves considering these diverse hypotheses, which offer potential targets for AD treatment.

According to the Aβ hypothesis, a toxic subtype of the protein Aβ—specifically $A\beta_{1\text{-}42}$—clumps together outside neurons to form harmful plaques. Meanwhile, τ-proteins form tangles inside brain cells due to excessive attachment of phosphate molecules. This mostly happens in areas of the brain that handle memory and emotions. The cholinergic hypothesis suggests that decreased levels of neurotransmitters, especially ACh, impair neuron communication, leading to cognitive decline. Additionally, metal imbalance and oxidative stress also contribute to the disease.[1,2]

Table 1 provides a detailed overview of the currently approved drugs by the United States Food and Drug Administration (FDA or US FDA), showing their target class, type of therapeutics, the inventor company, and the year of approval. Tacrine, acting on the cholinergic system, was the first approved drug back in 1993, while aducanumab and lecanemab, utilising immunotherapy-targeting Aβ, received approval in 2021 and 2023, respectively.[3,4] The recently approved monoclonal antibodies (mAbs) aim to change the underlying biology of the disease, while the rest of the approved molecules aim to improve AD symptoms.

Table 1. Currently approved drugs for Alzheimer's disease[a]

S No.	Drugs	Target	Therapeutics	Company Name	US FDA Approval
1	Tacrine[a,5]	Cholinergic system	Small molecule	Pfizer, Shionogi Pharma	1993
2	Donepezil[a,6]	Cholinergic system	Small molecule	Corium, Inc., Eisai Co., Ltd., Pfizer	1996
3	Rivastigmine[a,7]	Cholinergic system	Small molecule	Novartis Pharmaceuticals Corporation	1997
4	Galantamine[a,8]	Cholinergic system	Small molecule	Janssen, Ortho-McNeil Pharmaceutical, Sanochemia Pharmazeutika, Shire, Takeda Pharmaceutical	2001
5	Memantine[b,9]	Neurotransmitter antagonist of NMDA glutamate receptors in the brain	Small molecule	Forest Laboratories, Inc., Lundbeck, Merz Pharma	2003
6	Suvorexant[c,10]	Circadian rhythm (orexin receptor antagonist)	Small molecule	Merck	2020
7	Aducanumab[d,4]	β-amyloid	Immunotherapy (mAbs)	Biogen, Neurimmune	2021
8	Brexpiprazole[e,11]	Neurotransmitter (dopamine D2 receptor partial agonist)	Small molecule	Lundbeck, Otsuka Pharmaceutical Co., Ltd.	2023
9	Lecanemab[d,4]	β-amyloid	Immunotherapy (mAbs)	BioArctic AB, Biogen, Eisai Co., Ltd.	2023

Abbreviations: *AD, Alzheimer's Disease; mAbs, Monoclonal Antibodies; NMDA, N-methyl-D-aspartate; US FDA, United States Food and Drug Administration*
a Drugs inhibit the acetylcholinesterase enzyme;
b Inhibit the NMDA glutamate receptors;
a,b approved molecules that slow progression from moderate to severe AD;
c Suvorexant is approved for treating sleep disorders in AD;
d First approved mAbs, aim to change the underlying biology of the disease;
e Approved by US FDA for the treatment of agitation in AD.

Disease Epidemiology and Prevalence

According to World Alzheimer Report 2023, published by Alzheimer's Disease International, the number of people living with dementia worldwide is expected to rise from 55 million in 2019 to approximately 139 million by 2050.[12] This substantial shift in disease epidemiology and prevalence highlights the growing impact of dementia on a global scale.

The latest report of the Alzheimer's Association, published in 2023, reveals that an estimated 6.7 million Americans, aged 65 and older, are currently grappling with AD.[13] This figure is anticipated to surge to 13.8 million by 2060 unless there are advancements in medical breakthroughs to prevent, decelerate, or cure AD. Among the entire US population, approximately 1 in 9 individuals (10.8%) aged 65 years and above are affected by AD, which includes 5.0% of those aged 65-74, 13.1% of those aged 75-84, and 33.3% of those aged 85 years and older.[13]

While individuals under the age of 65 years can also develop AD, studies on its prevalence in the younger demographics are severely limited. Researchers estimate that 110 out of every 100,000 individuals between the ages of 30 and 64 years experience younger-onset dementia.[13] According to official data released by the National Center for Health Statistics, the year 2019 witnessed 119,399 recorded deaths attributed to AD, consequently ranking it as the seventh leading cause of death in the US.[14]

Clinical Landscape of Drugs in the Pipeline

Analysing the current pipeline of AD therapy is imperative due to the prolonged absence of novel treatment except for the recent approval of mAbs, aducanumab (2021) and lecanemab (2023) that change the underlying biology of the disease.[4,15,16] Notably, prior treatments including cholinesterase inhibitors [ChEIs], such as tacrine, donepezil, rivastigmine and galantamine, were approved between 1993 and 2001 and aimedonly to improve the symptoms **(Table 1).**[17] Memantine (2003) works by blocking NMDA glutamate receptors in the brain, also primarily aimed at improving only symptoms. Additionally other candidates like suvorexant (2020; approved for treating sleep disorders in AD) and brexpiprazole (approved for the treatment of agitation in AD) show potential, but the spotlight remains on aducanumab and lecanemab for their potential to alter disease progression.

The present analysis of the ClinicalTrials.gov database conducted in December 2023 reveals that there are currently 49 ongoing trials assessing 35 distinct interventions for treating AD. Among the 49 ongoing trials, 80% (39 trials) are currently in Phase III, while the remaining 20% (10 trials) are in Phase II/III. A majority of these ongoing trials, specifically 80% (39 trials), adopt a placebo-controlled design, while 14% (7 trials) are single-arm trials. Among the remaining three trials, one assessed donanemab versus aducanumab, another evaluated a non-drug treatment, and the third compared placebo with standard of care (SOC).

The National Institute on Aging and the Alzheimer's Association rely on Common Alzheimer's Disease Research Ontology (CADRO) to outline the biological processes in AD. Within the CADRO framework, the 'Translational Research and Clinical Interventions' category specifically identifies potential targets for clinical therapies aimed at addressing AD. Utilising the CADRO classification system, these 49 ongoing trials can be systematically arranged into nine distinct targets, as depicted in **(Figure 1)**. These include Aβ (n=13), neurotransmitter receptors (n=15), neuroprotection/synaptic plasticity (n=8), and metabolism/bioenergetics (n=5), along with five other targets (n=8). Additional analysis of ongoing trials shows that 49% (24 trials) assessed small molecules, 27% (13 trials) involved mAbs, 16% (eight trials) employed a combination of small molecules, 6% (three trials) incorporated biological peptides, and 2% (one trial) evaluated dietary supplements **(Figure 1)**.

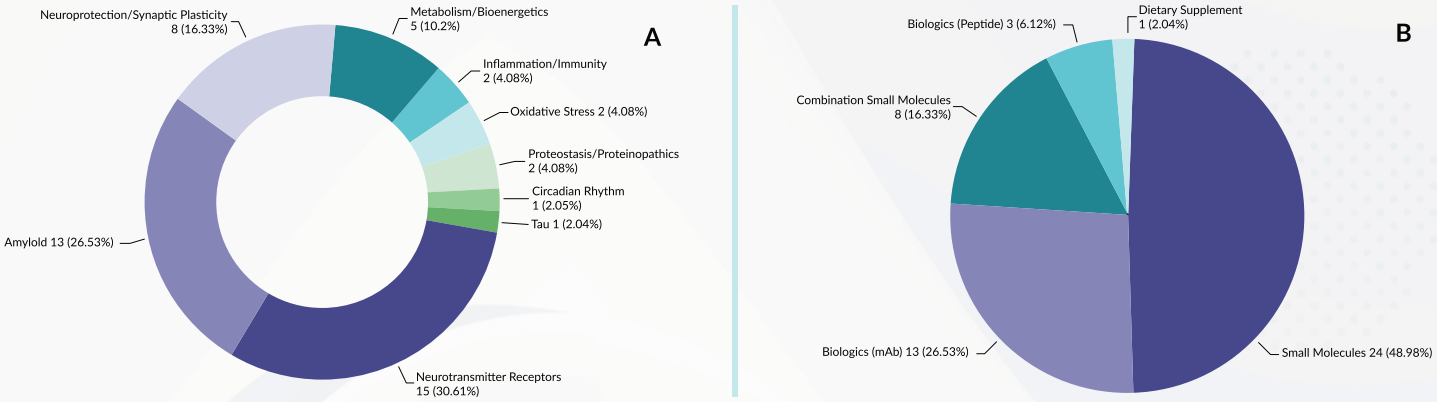
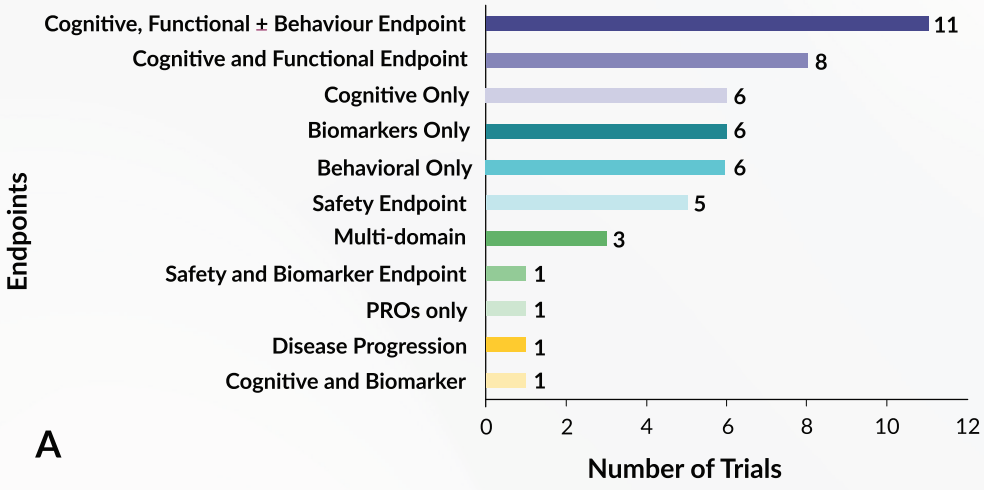


Figure 1. Nine distinct targets categorised according to the CADRO classification system (A) and therapy type for ongoing 49 trials (B)
Abbreviations: CADRO, Common Alzheimer's Disease Research Ontology; mAbs, Monoclonal Antibodies

Further examination revealed that the primary endpoints in these trials can be categorised into 11 groups **(Figure 2).** The predominant focus in the trials was on outcomes related to 'cognition-only' or 'cognitive, functional ± behavioural' aspects, constituting over 50% of the cases. This was followed by an emphasis on biomarkers (12%), behavioural-only (12%), safety (10%), multi-domain (6%), monitoring disease progression (2%), cognitive + biomarker (2%), patient-reported outcomes (PROs) only (2%), and safety and biomarker endpoint (2%). Additional analysis showed that 33 trials assessed the safety and efficacy of novel investigational molecules. Simultaneously, the remaining 16 trials explore the potential of US FDA-approved drugs for purposes beyond their initial indications, a process known as drug repurposing (**Figure 2B).** Among these repurposed drugs, four trials are currently assessing the two unique anti-diabetic drug molecules, semaglutide (Glucagon-like peptide 1- receptor agonist) and metformin (oxidative stress), sponsored by Novo Nordisk and Columbia University, respectively. The remaining 12 trials involve a diverse range of repurposed drugs for treating various diseases **(Figure 2B)**. Notably, a majority of these trials (74%) are sponsored by industry/pharmaceutical companies, with 16% receiving support from academic/research institutions, and 10% benefiting from dual academic and industry backing.



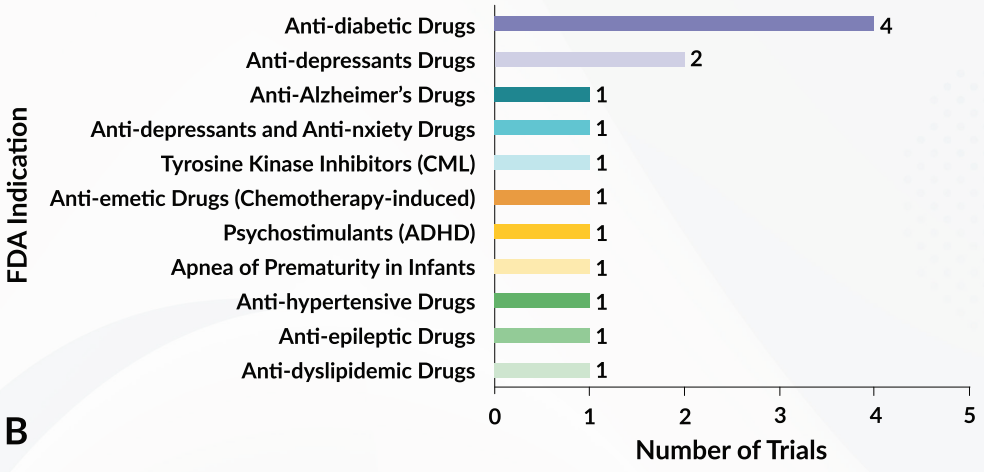


Figure 2. Primary endpoints employed in 49 ongoing trials categorised into 8 groups (A), alongside a detailed classification of investigational and repurposed molecules for the alzheimer's disease clinical trials (B) Abbreviations: *ADHD, Attention-Deficit/Hyperactivity Disorder; CML, Chronic Myelogenous Leukemia; PROs, Patient-Reported Outcomes*

Emerging Therapeutic Modalities

A transformative shift has occurred with the recent approval of two groundbreaking anti-amyloid mAbs: lecanemab and aducanumab, in the ever-evolving landscape of AD therapeutics. Unlike earlier treatments that targeted symptoms, these mAbs represent a paradigm shift by directly intervening in the fundamental biological processes of AD. Achieving accelerated approval from the US FDA, they stand as the first disease-modifying therapies capable of slowing AD progression.[4,15,16]

Two Phase III trials, EMERGE and ENGAGE, were conducted in subjects with mild cognitive impairment (MCI) and early AD to evaluate the efficacy of aducanumab.[18,19] The EMERGE study showed statistically significant changes in Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores, Mini-Mental State Examination scores, AD Assessment Scale-Cognitive Subscale version 13 (ADAS-Cog 13) scores, and AD Cooperative Study-Activities of Daily Living Scale for use in MCI (ADCS-ADL-MCI) scores for the high aducanumab dose only. Whereas the ENGAGE study failed to meet these same endpoints for both low and high aducanumab doses. The conflicting results in the EMERGE and ENGAGE trials have prompted Biogen to conduct ENVISION, a phase IIIb/IV clinical trial post-approval. This phase IV trial, which will be completed at the end of 2025, aims to determine whether aducanumab offers significant clinical benefit, highlighting ongoing uncertainties in AD therapeutics.[19,20]

Biogen's lecanemab is the second anti-amyloid antibody to receive fast-track approval and the first to receive full approval by the US FDA. The Clarity AD trial for lecanemab also achieved the primary endpoint, measured by CDR-SB scores, indicating a 27% reduction in cognitive decline with lecanemab after 18 months of treatment compared with those who received a placebo. The lecanemab group also exhibited significant results across key secondary endpoints such as amyloid burden on positron emission tomography (PET), improvements in ADAS-Cog14, AD Composite Score, and the ADCS-ADL-MCI.[21]

Failure and Lessons Learned

AD stands as one of the most challenging therapeutic areas for drug development, characterised by an exceptionally high failure rate, nearing 100%.[22] In the period spanning from 1995 to 2021, the US FDA approved 878 drugs across diverse therapeutic areas, with a mere six indicated for AD i.e., four ChEIs, memantine, and aducanumab.[23] Notably, brexpiprazole and lecanemab received approvals in 2023, adding to this small roster **(Table 1).**[14,16,21]

An investigation of the ClinicalTrials.gov database revealed that a staggering 83 trials in Phase II/III or III faced termination, suspension, or an unknown status until Dec 2023. The primary causes for discontinuation were: inability to meet the efficacy endpointsin 40% (33 trials) of trials, safety concerns in 2% (2 trials), a combination of both safety and efficacy issues in 12% (10 trials), challenges in recruiting a substantial number of subjects 8% (7 trials), and unknown status 23% (19 trials). Additionally, 15% (n=12) of the trials were discontinued due to other unspecified reasons **(Figure 3A).** Simultaneously, the database also documented 125 clinical trials in Phase II/III or III with the completed status. The analysis of linked trial publications revealed that 28 of the completed trials failed to meet their efficacy endpoints, four failed to meet both safety and efficacy endpoints, and one trial had serious safety issues **(Figure 3B).** A subsequent analysis of the 125 completed trials showed that 35.2% (44) of trials had unknown status due to the absence of posted results or linked publications disclosing the trial outcomes. Additionally, the analysis also highlighted that 31.2% (39) completed trials featured interventions already approved for AD **(Figure 3B)**. These approved interventions primarily comprised distinct formulations/dose variations/salts of donepezil, rivastigmine, galantamine, memantine, and brexpiprazole.

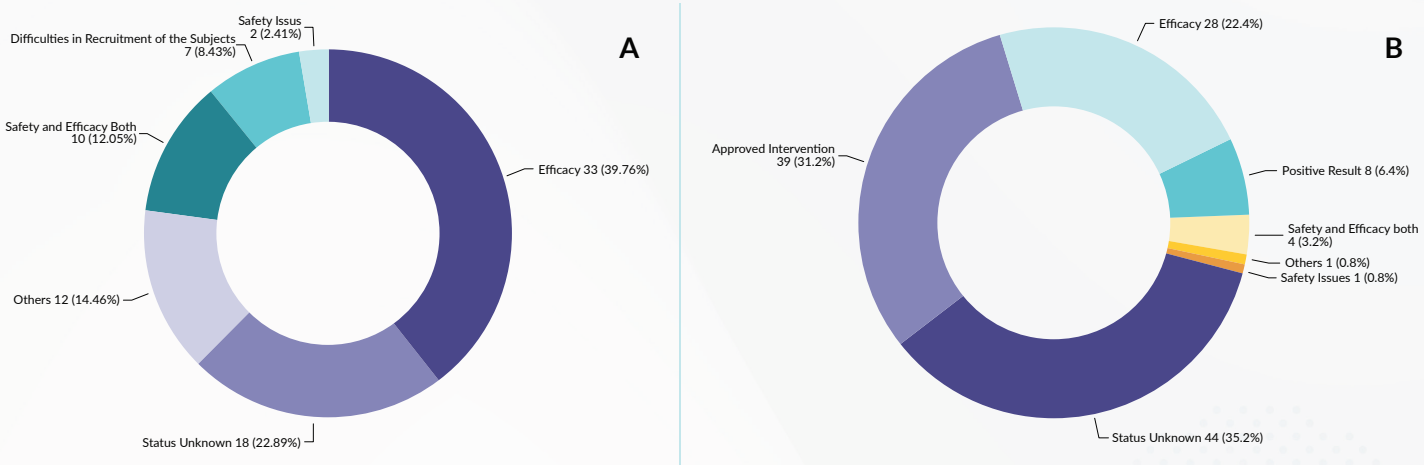


Figure 3. The underlying reasons for termination, suspension, or an unknown status of trials in the ClinicalTrials.gov database for Alzheimer's disease (A), and the status of completed Phase II/III or III clinical trials for Alzheimer's disease retrieved from the ClinicalTrials.gov database (B)

Having explored the challenges encountered by numerous AD trials sourced from ClinicalTrials.gov database, it becomes evident that a high rate of termination and suspension is of significant concern. This emphasizes the crucial need to ensure trials are designed with sensitive and clinically relevant endpoints. Cognitive decline, a hallmark of AD, has traditionally been a primary focus for trial endpoints. However, there's also a growing recognition of the significance of assessing functional outcomes and measuring biomarkers as endpoints, especially in trials targeting the early stages of AD. Biomarkers, such as amyloid measurement—a hallmark of AD—that misfold and accumulate in the brain, forming plaques, were key endpoints for the recently approved mAbs lecanemab and aducanumab.[24]

As previously discussed, the trials' inability to meet the efficacy endpoint emerged as one of the major reason for their termination/suspension. This signifies the pivotal role played by the US FDA in guiding the selection of the trial endpoints. Over the last decade, the US FDA has released two crucial guidelines for AD trials focusing on primary endpoint selection. In 2013, a draft guidance recommended the use of composite cognitive and functional scores, such as CDR-SB, to measure mild cognitive improvement in early-stage AD trials. [25] Subsequently, in 2018, the US FDA updated its guidance to advocate for a broader array of endpoints, including biomarkers, coprimary endpoints, and integrated scales (i.e., cognitive and functional) stages of AD.[26] Although these guidelines are influential, it's essential to note that they remain non-binding. The impact of this US FDA guidance is evident in the evolution of AD drug development. Research indicates a significant increase in the annual use of cognitive/functional composite endpoints after the 2013 guidance (+12.9%, P<0.001).[24] However, a subsequent decrement in the selection of cognitive/functional composite endpoints was noted after the 2018 guidance (-19.9%, P=0.022).[24] This dynamic interplay between regulatory guidance and trial design emphasises adapting strategies based on evolving disease insights and recommendations.[24]

Recruiting participants for AD clinical trials is another challenge, particularly with the complex eligibility process lasting 30 to 60 days. Cognitive testing and neuroimaging before subject recruitment demands commitment from patients and their families. The use of placebo groups, while crucial, deters enrolment due to the potential for 18-month trial periods leading to disease worsening. Most clinical trials require patients with early AD but, in general, patients are diagnosed late and are often too far along in their disease course to participate in a clinical trial. These late-stage diagnoses hinder trial participation, requiring the implementation of better education initiatives and increased responsiveness from healthcare providers and institutions. Successful trials necessitate accessible screenings and understanding from participants, caregivers, and payers.

Insights Into Health Economics and Market Access

Understanding the cost-effectiveness and the financial burdens reveals critical insights into economic and market challenges surrounding AD treatment. The economic evaluation of AD conducted by Eroymak et al. emphasizes that diagnosing and treating AD in its early stages is the most cost-effective option compared to treating severe stages. This approach potentially offers significant benefits in both social and monetary terms.[27] The study was conducted in Turkey from the perspective of the Social Security Institution. Eroymak et al. used gross domestic product (GDP) as the threshold value, following the recommendation of the World Health Organization. Moreover, the study revealed that the mean survival time and quality of life in patients with AD, treated at early and moderate stages, were higher than those in patients being treated at the severe stage.[27]

Ross et al. conducted a cost-effectiveness analysis comparing the recently approved mAb, aducanumab, to standard care for early AD in the US.[28] The model utilised aducanumab's base price of $20,500 per year for the first year and $28,200 per year thereafter. The study indicates that, at the current price, aducanumab may not be deemed cost-effective for treating early AD in the US. To achieve cost-effectiveness, the price of aducanumab would need to decrease to less than $3,000 per year.[28]

The financial burden associated with the healthcare and long-term care of individuals diagnosed with AD is substantial, rendering dementia one of the most economically impactful conditions to society.[27] The total projected expenditure for individuals impacted by AD or other dementias in the US reached $345 billion in 2023, with projections suggesting a potential increase to under $1 trillion by the year 2050.[13] Medicare is poised to contribute $157 billion, constituting 45% of the total health care and long-term care payments **(Figure 4)**. Concurrently, Medicaid is anticipated to have $65 billion, representing 19% of the financial allocation while out-of-pocket and other funding sources contribute $87 billion and $37 billion, respectively, making up 25% and 11% of the total expenditures **(Figure 4).**[13]

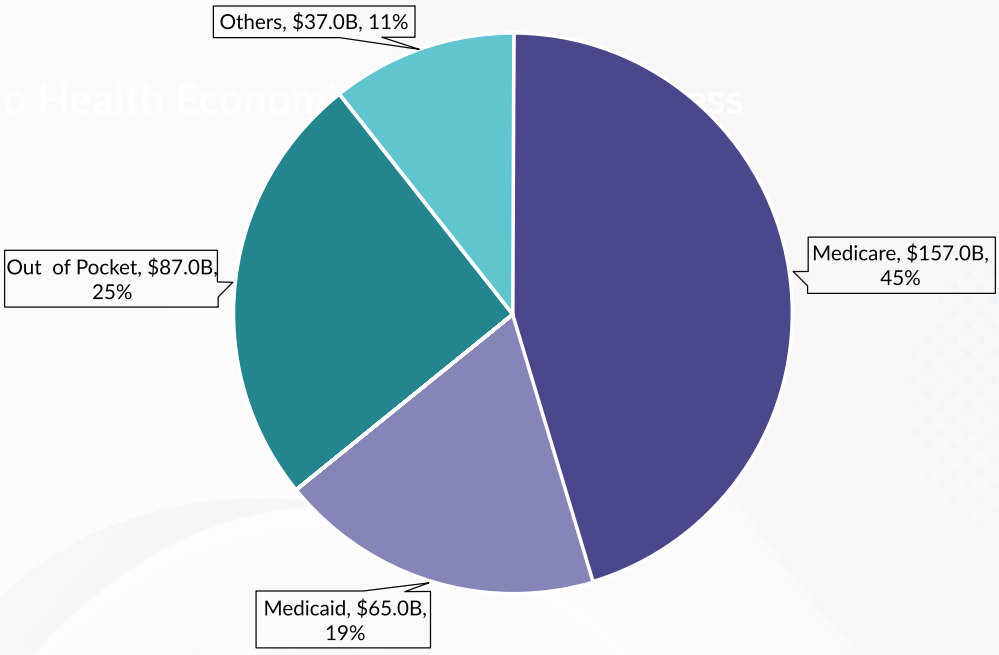


Figure 4. Distribution of care costs (in Billion USD) for Americans aged 65 and older with Alzheimer's disease or other dementia by payment source

According to the European Alzheimer's Disease Consortium- European Commission viewpoint, an estimated 5.4 million individuals in 27 European Union countries will be eligible for treatment with another recently approved mAbs, lecanemab.[30] However, if this drug is priced similarly to its cost in the US, the annual treatment expenses are projected to surpass €133 billion. This figure represents over half of the total pharmaceutical expenditures in the European Union, rendering the therapy financially unsustainable. The potential financial burden could make the drug unattainable for patients in some European regions, prompting considerations about the affordability and feasibility of widespread treatment.[30]

Overall, the escalating financial impact of AD on healthcare and long-term care, along with the evolving landscape of treatment costs, highlights the urgent need for sustainable and accessible solutions. The projected expenditures, both in the US and the European Union, reflect not only the immense economic strain on the healthcare system but also the imperative for strategic pricing and policy considerations. Addressing these issues with foresight and collaborative efforts is crucial to ensuring equitable access to effective treatments for individuals affected by AD in the years ahead.

Concluding Remarks

In conclusion, the landscape of AD therapeutics is rapidly evolving, as indicated by the dynamic array of interventions currently under investigation. With a substantial pipeline of 49 trials assessing 35 distinct interventions, mainly in Phase III, there is a clear emphasis on addressing the complex challenges of AD through diverse methodologies and therapeutic modalities. These efforts, spanning small molecules, mAbs, and drug repurposing, reflect astrategic approach to combating this debilitating disease. Recent milestones such as the US FDA approvals of aducanumab and lecanemab mark a transformative phase in AD therapeutics. Despite the controversy surrounding aducanumab's approval, ongoing studies like ENVISION aim to address uncertainties surrounding its clinical efficacy. Similarly, the success of lecanemab in the Clarity AD trial highlights the progress in targeting fundamental biological processes to reduce cognitive decline. However, challenges persist in AD drug development, as evidenced by the high failure rate of clinical trials and the limited number of US FDA-approved drugs over the past few decades. The analysis of ClinicalTrials.gov data reveals a significant number of trials facing termination or suspension.

Regulatory guidance, particularly from the US FDA, plays a vital role in shaping trial design, yet the non-binding nature of guidelines necessitates adaptive strategies based on evolving insights. These guidances emphasize the crucial need for selecting sensitive endpoints and incorporating functional outcomes and biomarkers alongside cognitive decline assessments. Moreover, recruitment of participants remains a hurdle due to complex eligibility processes and the use of placebos.

In navigating these challenges, it is essential to adopt a holistic approach, incorporating evolving science, adaptive study designs, and enhanced engagement. The diverse and innovative landscape of AD therapeutics, coupled with ongoing research and regulatory efforts, offers optimism for the future. By addressing these challenges collaboratively and strategically, we can move closer to realizing effective treatments for AD and improving the quality of life for millions affected by this disease.

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