Mapping the Current Clinical Landscape for Alzheimer's Disease: A Qualitative Analysis

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BACKGROUND AND OBJECTIVE

- Alzheimer's disease (AD) is a progressive neurodegenerative disorder that impairs memory, language skills, behavior, and thinking.[1,2]
- According to the 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.[3]
- The prolonged absence of novel treatments for AD prompted us to examine the present clinical pipeline of AD therapies.[4]
- This study aimed to analyze the current clinical landscape of AD therapies in terms of types of interventions being evaluated in ongoing trials, the classification of these interventions according to Common Alzheimer's and Related Dementias Research Ontology (CADRO) targets, primary endpoints assessed in these trials, and the status of Phase II/III or III trials.
- We also aimed to explore reasons for the termination or suspension of trials and the distribution of approved AD interventions among the completed trials.

METHOD

- ClinicalTrials.gov was searched for trials assessing AD up to 04 December 2023.
- Trials assessing non-pharmacologic intervention, diagnostic agents, and different trial methodologies were excluded.
- Ongoing trials and trials with completed/terminated/suspended/unknown/withdrawn status were analyzed separately.

RESULTS

- The analysis of the ClinicalTrials.gov database identified 322 trials, of which 257 met the inclusion criteria. Of these, 49 were ongoing (as of 04 Dec 2023), 125 were completed, and 83 had terminated/suspended/unknown/withdrawn status.

Ongoing Trials

- The ongoing 49 trials assess 35 unique interventions for the treatment of AD.
- Among these 49 ongoing trials, 80% (39 trials) are currently in Phase III, while the remaining 20% (10 trials) are in Phase II/III.
- Majority of the ongoing trials, i.e., 80% (39 trials), adopt a placebo-controlled design, while 14% (seven 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) (**Figure 1**).
- Utilizing the CADRO classification system, these 49 ongoing trials were systematically arranged into nine distinct targets, as depicted in **Figure 2A**. These include neurotransmitter receptors (n=15), Aβ (n=13), 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 monoclonal antibodies (mAbs), 16% (eight trials) employed a combination of small molecules, 6% (three trials) incorporated biological peptides, and 2% (one trial) evaluated dietary supplements (**Figure 2B**).

Figure 1. Types of comparators assessed in ongoing trials

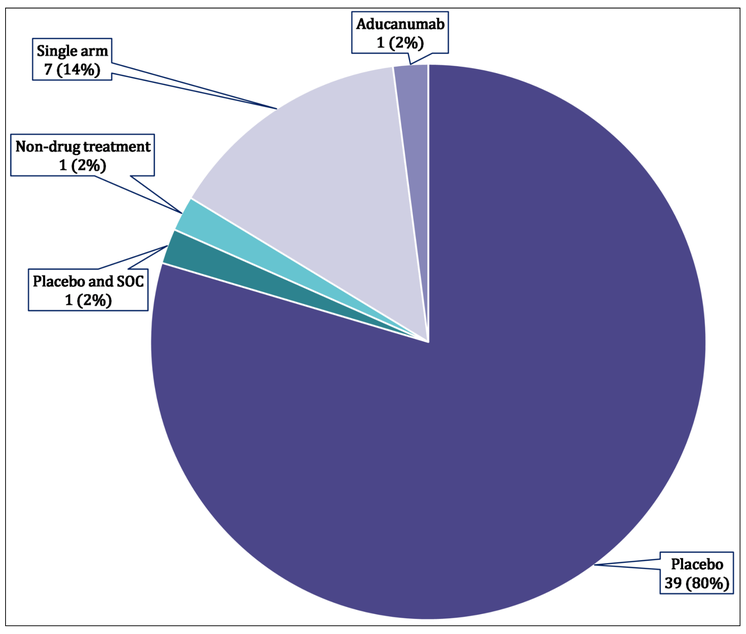
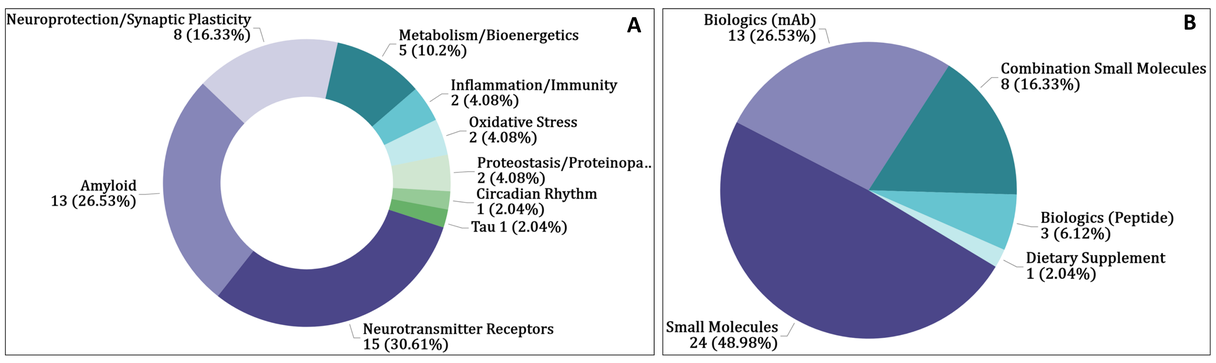


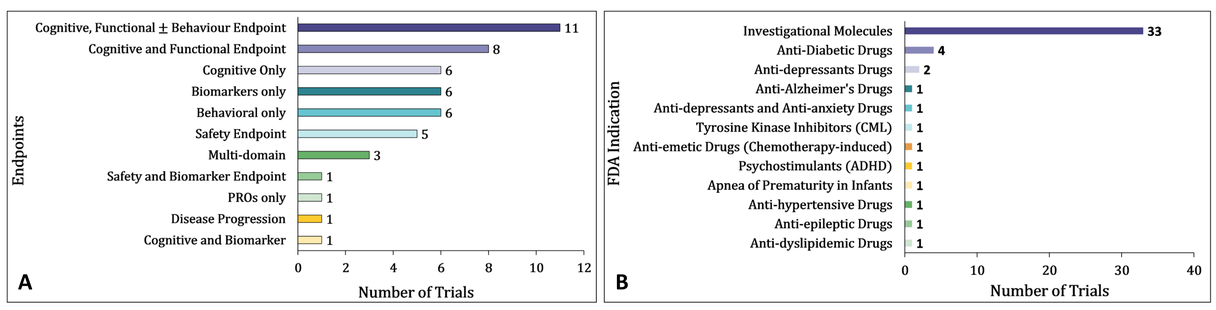
Figure 2. Nine distinct targets categorized according to the CADRO classification system (A) and therapy type for ongoing 49 trials (B)



Abbreviations: CADRO: Common Alzheimer's Disease Research Ontology; mAbs: Monoclonal Antibodies.

- Further examination revealed that the primary endpoints in these trials can be categorized into 11 groups (**Figure 3A**). The predominant focus in the trials was on outcomes related to "cognition-only" or "cognitive, functional ± behavioral" aspects, constituting over 50% of the cases. This was followed by an emphasis on biomarkers (12%), behavioral-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 assess 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 3B**).
- Among trials assessing these repurposed drugs (n=16), four trials are currently assessing the two unique anti-diabetic drug molecules, semaglutide (Glucagon-like peptide 1- receptor agonist) and metformin (oxidative stress). The remaining 12 trials assess a diverse range of repurposed drugs for treating various diseases (**Figure 3B**).

Figure 3. Primary endpoints employed in 49 ongoing trials categorized into 11 groups (A), alongside a detailed classification of investigational and repurposed molecules for the Alzheimer's disease clinical trials (B)



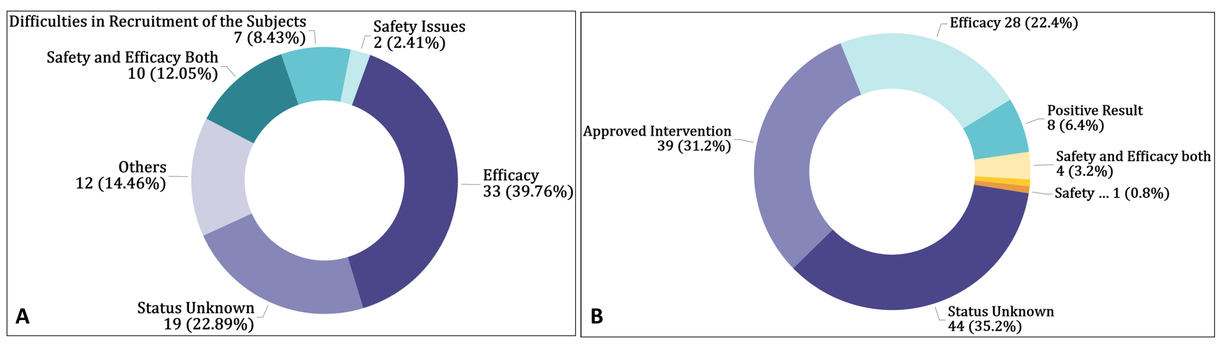
Abbreviations: ADHD: Attention-Deficit/Hyperactivity Disorder; CML: Chronic Myelogenous Leukemia; PROs: Patient-Reported Outcomes

- Notably, majority of these trials (74%) are sponsored by industry/pharmaceutical companies, 16% received support from academic/research institutions, and 10% benefitted from dual academic and industry backing.

Trials with Terminated/Suspended/Unknown/Withdrawn and Completed Status

- The investigation of the ClinicalTrials.gov database also revealed that 83 out of a total 257 trials in Phase II/III or III faced termination, suspension, or have an unknown status.
- The primary causes for discontinuation were – inability to meet the efficacy endpoints in 40% (33 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% (12 trials) of the trials were discontinued due to other unspecified reasons (**Figure 4A**).
- A subsequent analysis of the 125 completed trials showed that 35.2% (44) of trials had unknown status due to results not being posted or linked publications disclosing the trial outcomes.
- Additionally, the analysis also highlighted that 31.2% (39 trials) completed trials featured interventions already approved for AD. These approved interventions primarily comprised distinct formulations/dose variations/salts of donepezil, rivastigmine, galantamine, memantine, and brexpiprazole (**Figure 4B**).

Figure 4. Underlying reasons for termination, suspension, or an unknown status of trials in the ClinicalTrials.gov database (A) and the status of completed Phase II/III or III clinical trials retrieved from the ClinicalTrials.gov database (B)



CONCLUSIONS

- The findings reveal a diverse pipeline for AD drug development in terms of targets and treatment modalities.
- Nonetheless, amyloid and neurotransmitter receptor targeting continues to be prominent therapeutic strategy for AD treatment.
- Despite this diversity, the study highlights challenges in meeting efficacy endpoints and gaps in AD drug development, emphasizing the need for innovative solutions.

FUNDING

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