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RESEARCH ARTICLE

Alzheimer's disease drug development pipeline: 2021

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Abstract

Introduction: The number of individuals worldwide with Alzheimer's disease (AD) is growing at a rapid rate. New treatments are urgently needed. We review the current pipeline of drugs in clinical trials for the treatment of AD.

Methods: We interrogated ClinicalTrials.gov, the federal registry of clinical trials to identify drugs in trials.

Results: There are 126 agents in 152 trials assessing new therapies for AD: 28 treatments in Phase 3 trials, 74 in Phase 2, and 24 in Phase 1. The majority of drugs in trials (82.5%) target the underlying biology of AD with the intent of disease modification; 10.3% are putative cognitive enhancing agents; and 7.1% are drugs being developed to reduce neuropsychiatric symptoms.

Discussion: This pipeline analysis shows that target biological processes are more diversified, biomarkers are more regularly used, and repurposed agents are being explored to determine their utility for the treatment of AD.

KEYWORDS
Alzheimer's disease, amyloid, biomarkers, clinical trials, Common Alzheimer's Disease Research Ontology (CADRO), drug development, inflammation, National Institutes of Health, pharmaceutical companies, repurposed drugs, tau

1 | INTRODUCTION

Alzheimer's disease (AD) is the sixth leading cause of death in the United States and the fifth leading cause among those over age 65. The current number of those with AD dementia is 5.8 million and this is anticipated to grow to 13.8 million in 2050 if effective interventions are not found. Based on 2018 death certificate data, 122,019 individuals succumbed from AD dementia that year, indicating an average daily death toll of 334.[1] AD dementia is preceded by a preclinical phase that may last for 15 to 20 years and a prodromal period that persists for 3 to 6 years prior to onset of dementia.[2] Preclinical, prodromal, and AD dementia are all populations in which clinical trials are ongoing; the US Food and Drug Administration (FDA) has provided guidance on defining AD populations from preclinical to late-stage dementia to facilitate clinical trials and drug development across the continuum of AD.[3]

The biology of AD is increasingly well understood and comprises a plethora of complex, progressive, interactive, destructive processes leading to cell dysfunction and death.[4] The Common Alzheimer's Disease Research Ontology (CADRO) provides a means of classifying targets for drug development relevant to AD.[5] There is an urgent need to develop new therapies for disease modification of AD and to address cognitive impairment and neuropsychiatric symptoms with symptom-reducing agents. Progress is being made. Suvorexant had a successful Phase 3 trial for insomnia in AD and safety and efficacy data have been added to the package insert allowing clinicians to use this agent for sleep disturbances in AD using evidence-based guidance.[6] Pimavanserin is under review by the FDA for treatment of dementia-related psychosis,[7] and aducanumab is under review for treatment of progression of AD.[8] Regardless of the outcomes of these regulatory reviews, the trials and development data packages have advanced adequately

to warrant regulatory review and indicate increasing confidence in trials to demonstrate efficacy and safety of AD therapeutics.

We conduct an annual review of the AD drug development pipeline with the intent of understanding the progress of the field in developing new therapeutics including new agents, targets, biomarkers, and trial design strategies.[9–13] Here we present the results of our analysis of the 2021 pipeline as represented on ClinicalTrials.gov.

2 | METHODS

We used the FDA/US National Library of Medicine of the National Institutes of Health (NIH) clinical research registry, ClinicalTrials.gov, as the source of information for this review. The "common rule" governing ClinicalTrials.gov specifies that registration is required for studies that meet the definition of an "applicable clinical trial" (ACT) and were initiated after September 27, 2007 or initiated on or before that date and were still ongoing as of December 26, 2007. ACTs, as defined in section 402(j) of the Public Health Service Act, include controlled clinical investigations of any FDA-regulated drugs, biological therapies, or devices for any disease or condition. ACTs generally include interventional studies (with one or more arms) of FDA-regulated products that meet one of the following conditions: the trial has one or more sites in the United States; the trial is conducted under an FDA investigational new drug application exemption; or the trial involves a small molecule drug, biological therapy, or device that is manufactured in the United States or its territories and are studied for research purposes.[14] Studies of ClinicalTrials.gov suggest that compliance with the common rule is high.[15,16] The reporting of results of clinical trials is required, but trial sponsors are less adherent to this expectation.[17] The United States has more clinical trials than any other country, and ClinicalTrials.gov includes the majority of agents currently in clinical trials for AD; this review is therefore comprehensive but not exhaustive. There are other clinical trial registries and comparisons show that only a few agents registered in the European Union Clinical Trial Register, for example, are not found on ClinicalTrials.gov.[18] Phase 1 trials are often conducted outside of the United States, may not be registered on ClinicalTrials.gov, and may be under-represented in our analysis.

This review is based on trials present on ClinicalTrials.gov as of January 5, 2021; the tables and text of the review apply to the information available at that time. We comment on terminated trials if the information has become publicly available but is not yet reflected on ClinicalTrials.gov. We include all trials of agents in Phase 1, 2, and 3; if trials are presented as Phase 1/2 or Phase 2/3 in the ClinicalTrials.gov database we use that terminology in the review. We collect information on the trial agent; trial title; trial number in ClinicalTrials.gov; start date; projected end date; actual end date, if completed or terminated; primary completion date; calculated trial duration; duration of treatment exposure; number of subjects planned for enrollment; number of arms of the study (usually a placebo arm and one or more treatment arms with different doses); whether a biomarker was described; whether the agent was repurposed; subject characteristics (age range, acceptable range of cognitive impairment, etc.); and sponsorship (a biopharmaceutical company, NIH with academic medical centers, public–private partnership, or "other"). We included trials labeled as recruiting, active but not recruiting (e.g., trials that have completed recruitment and are continuing with the exposure portion of the trial), enrolling by invitation (e.g., open-label extensions of trials), and not yet recruiting. We did not include trials listed as completed, terminated, suspended, unknown, or withdrawn as information on these trials and reasons for their current status are often not publicly revealed. We do not include trials

RESEARCH IN CONTEXT

1. **Systematic review:** We reviewed drugs currently in clinical trials and registered in the mandated federal database, ClinicalTrials.gov.
2. **Interpretation:** There are 126 agents in clinical trials in 2021; the total number of treatments in trials is similar in 2021 and 2020. Most drugs in trials aim to achieve disease modification by targeting the underlying biological processes of Alzheimer's disease (AD). Understanding of the continuum of AD from preclinical stages to severe dementia is reflected in broadening of the trial populations to include preclinical AD, prodromal AD, and AD dementia. Repurposed agents play an important role in the pipeline, especially in Phase 2 trials. Trial participants make an enormous contribution to clinical trials (calculated to be ≈2.5 million participant-weeks for currently ongoing trials) and research partners invest a similar amount of time in trials.
3. **Future directions:** To develop urgently needed drugs with timely delivery to the market, trials must be shorter, smaller, and less expensive. Use of biomarkers and more targeted clinical outcomes as well as improvements in trial site performance will contribute to achieving this goal. If new therapies are approved by regulatory authorities, more sponsors and more funding may be attracted to AD research with accelerated innovation.

HIGHLIGHTS

- There are 126 agents in clinical trials for Alzheimer's disease.
- Most of the agents in the trial target disease modification.
- More than 38,000 participants are required for currently registered trials; cumulatively they will contribute more than 2.5 million participant-weeks in trials.
- Across all trials, biopharmaceutical companies sponsor 49% of trials and collaborate in another 14% of trials sponsored by public–private partnerships.

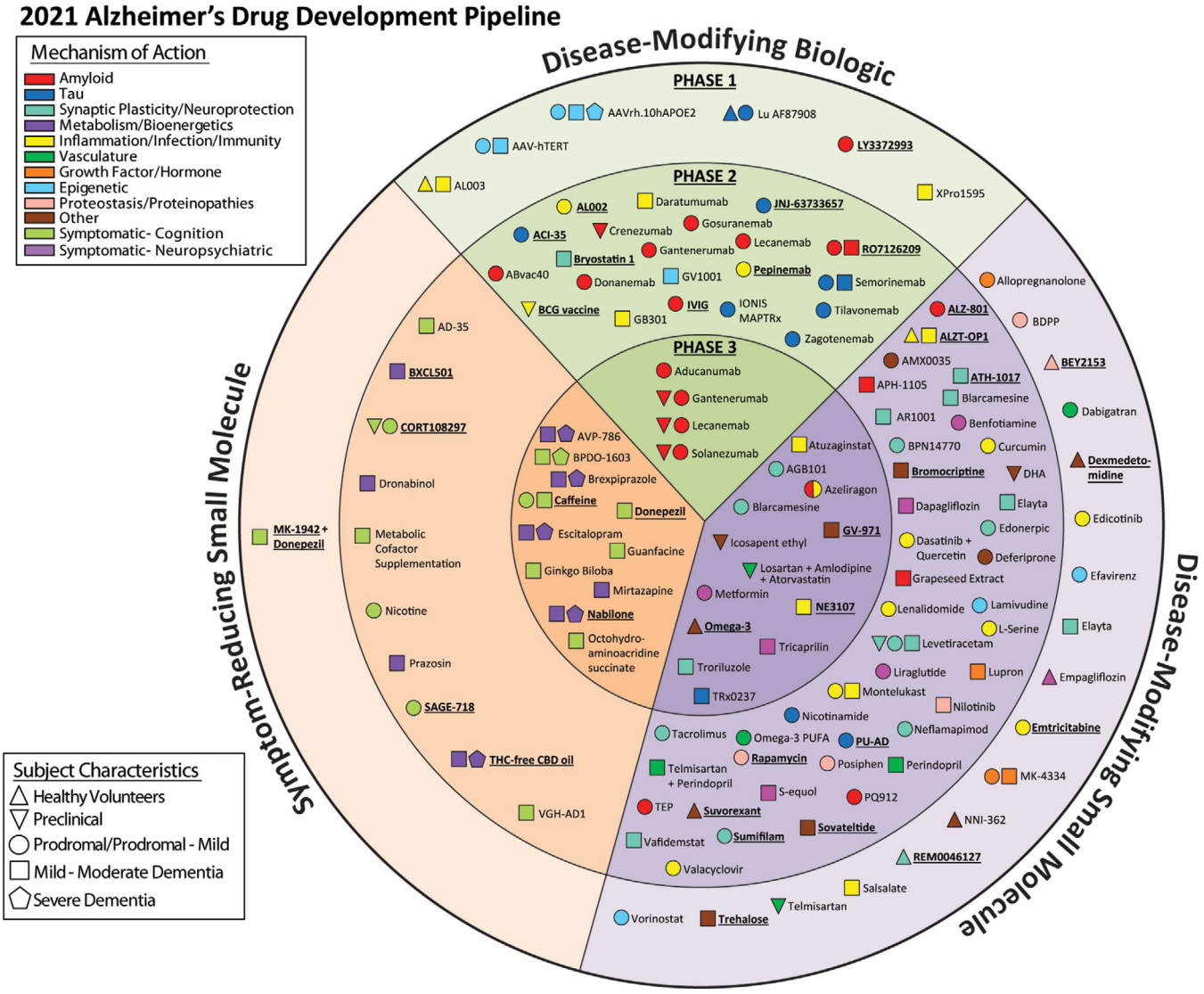

FIGURE 1 Agents in clinical trials for treatment of Alzheimer's disease in 2021 (from ClinicalTrials.gov as of the index date of January 5, 2021). The inner ring shows Phase 3 agents; the middle ring comprises Phase 2 agents; the outer ring presents Phase 1 therapies; agents in green areas are biologics; agents in purple are disease-modifying small molecules; agents in orange are symptomatic agents addressing cognitive enhancement or behavioral and neuropsychiatric symptoms; the shape of the icon shows the population of the trial; the icon color shows the Common Alzheimer's Disease Research Ontology (CADRO)-based class of the agent ("Other" category includes CADRO classes that have three or fewer agents in trials). Agents underlined are new to the pipeline since 2020. Figure: J Cummings; M de la Flor, PhD, Illustrator

of non-pharmacologic therapeutic approaches such as cognitive therapies, caregiver interventions, supplements, and medical foods. We do not include trials of biomarkers; we note whether biomarkers were used in the trials discussed. We include stem cell therapies among the interventions reviewed (they are not integrated into Figure 1).

For mechanism of action (MOA), we classified agents using the CADRO[5] approach. Some agents have more than one mechanism of action and, in these cases, we noted both mechanisms and depended on the available literature to identify a dominant mechanism. We use the terminology of "symptomatic" treatments for agents whose purpose was cognitive enhancement or control of neuropsychiatric symptoms without claiming to impact the biological causes of cell death in AD, and we used the terminology of "disease-modifying" for treatments that intended to change the biology of AD and produce neuroprotection (often through a variety of intermediate mechanisms such as effects on amyloid or tau).[19] We used the features of the trials (e.g., clinical outcomes, trial duration, use of biomarkers, number of participants) to determine whether a trial was attempting to demonstrate disease medication or symptomatic benefit. We recognize that these definitions are arbitrary, and many therapies may have symptomatic and disease-modifying effects. We divided disease-modifying therapies (DMTs) into biologics and small molecules. Biologics are generally derived from living organisms and include antibodies, vaccines, antisense oligonucleotides (ASOs), and therapeutic proteins. "Small molecules" refers to drugs typically taken orally that are <500 daltons in size and can regulate a biological process. AD has preclinical, prodromal, and

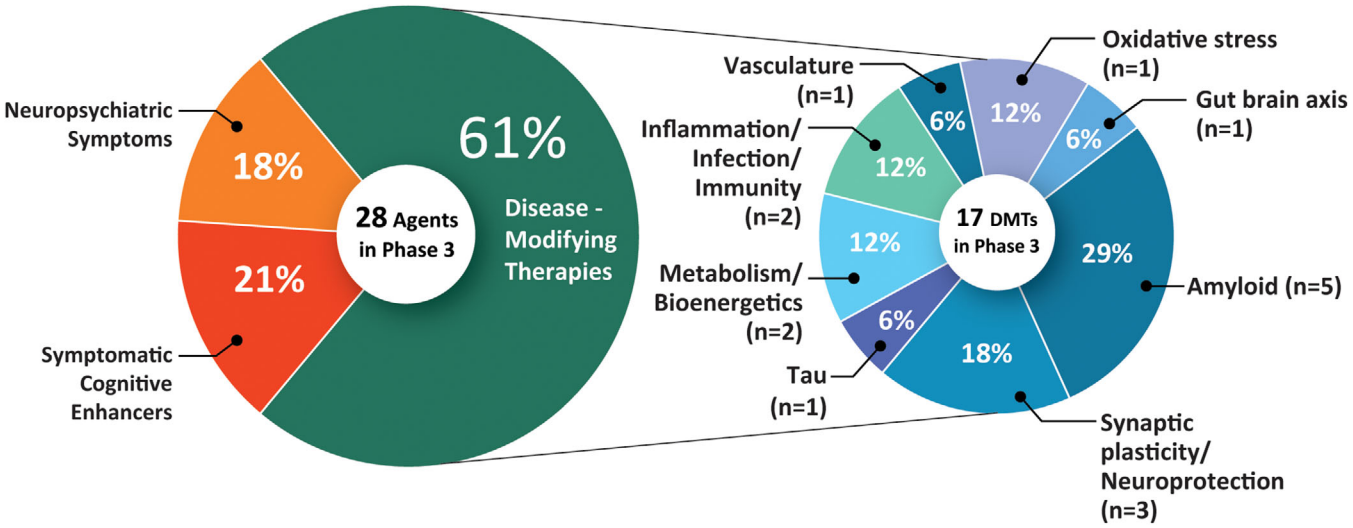

FIGURE 2 Mechanisms of action of agents in Phase 3 (as classified using the Common Alzheimer's Disease Research Ontology approach). Figure: J Cummings; M de la Flor, PhD, Illustrator

dementia phases,[20] and we note if the studies are prevention trials including participants with preclinical AD; prodromal trials with participants with mild cognitive impairment (MCI) who have biomarker evidence indicative of AD pathology; or have mild, moderate, or severe AD dementia.

3 | RESULTS

3.1 | Overview

There were 126 agents in 152 trials of treatments for AD (as of the index date of January 5, 2021). Twenty-eight agents are in 41 Phase 3 trials, 74 agents are in 87 Phase 2 trials, and 24 agents are in 24 Phase 1 trials. Figure 1 shows all pharmacologic compounds currently in clinical trials for AD. DMTs are the most common agents being studied (104; 82.5% of the total number of agents in trial); 13 (10.3%) agents in trials target cognitive enhancement; and 9 (7.1%) are intended to treat neuropsychiatric and behavioral symptoms. Of the DMTs 16 (15.4%) have amyloid and 11 (10.6%) have tau as the primary target or as one of several potential effects. Considering DMTs only, there are 17 in Phase 3, 64 in Phase 2, 23 in Phase 1. Across all phases, DMTs comprise 31 (29.8%) biological therapies and 73 (70.2%) small-molecule drugs. There are 50 repurposed agents in the pipeline—39.6% of the candidate agents.

3.2 | Phase 3

In Phase 3 there are 28 agents in 41 trials (Figure 1, Figure 2, Table 1). There are 11 (39.3%) symptomatic agents in Phase 3: six (21.4%) cognitive enhancers and five (17.9%) targeting behavioral symptoms. There are 10 repurposed agents in Phase 3 trials. Among the 17 DMTs there are four biological therapies and 13 oral agents/small molecule therapies. All four of the biological therapies and one of the small molecules—four monoclonal antibodies and one receptor for advanced glycation end products (RAGE) antagonist—have amyloid as the primary or one of several targets (29.4% of DMTs). Other CADRO mechanisms represented among Phase 3 DMT therapies include tau (one agent; 5.9% of Phase 3 DMTs), inflammation/infection (two agents; 11.8%), oxidative stress (two agents; 11.8%), metabolism and bioenergetics (two agents; 11.8%), vascular factors (one agent; 5.9%), synaptic plasticity/neuroprotection (three agents; 17.6%), and gut–brain axis (one agent; 5.9%). Figure 2 shows the MOAs of agents in Phase 3. Four (23.5%) of the DMT agents in Phase 3 are repurposed agents approved for use in another indication. Since the 2020 review, seven Phase 3 trials have been completed or terminated and there are five new agents in this phase.

There were five Phase 3 prevention trials enrolling cognitively normal participants known to be at risk for AD (preclinical AD). Two of these trials are assessing monoclonal antibodies (solanezumab, gantenerumab), there is one vaccine trial (CAD106), and two trials of small molecules (icosapent ethyl and a combination of losartan, amlodipine, and atorvastatin). There is one Phase 3 trial enrolling both preclinical patients and patients with MCI to mild AD dementia (DIAN-TU trial); 13 trials in patients with prodromal AD/MCI or prodromal/mild AD dementia; 11 trials of patients with mild to moderate AD; and 11 trials of patients with mild-to-severe AD (most of the neuropsychiatric agents).

Phase 3 trials included a mean of 619 participants per trial and a total of 25,373 participants were needed for enrollment. Prevention trials included a mean of 684 participants and had a mean duration of 335 weeks (including the recruitment and the treatment period). DMT trials focusing on prodromal AD or prodromal AD/mild AD dementia had a mean of 772 participants and a mean duration of 240 weeks (including the recruitment and the treatment period).

TABLE 1 Agents in Phase 3 of Alzheimer's disease drug development (ClinicalTrials.gov accessed January 5, 2021)

Agent	CAD ROMechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Aducanumab	Amyloid	Monoclonal antibody directed at Aβ plaques and oligomers	DMT	Enrolling by invitation (NCT04241068)	Biogen	Mar 2020	Oct 2023
AGB101 (low-dose levetiracetam)	Synaptic Plasticity/Neuroprotection	SV2A modulator; to reduce Aβ-induced neuronal hyperactivity	DMT	Recruiting (NCT03486938)	AgeneBio, NIA	Jan 2019	Dec 2022
Atuzaginstat (COR388)	Inflammation/Infection	Bacterial protease inhibitor targeting gingipain produced by *P. gingivalis* to reduce neuroinflammation and hippocampal degeneration	DMT	Active, not recruiting *(NCT03823404)	Cortexyme	Mar 2019	Dec 2022
AVP-786	Neurotransmitter receptors	Sigma 1 receptor agonist; NMDA receptor antagonist	Neuropsychiatric symptoms agent (agitation)	Recruiting (NCT03393520)	Avanir	Oct 2017	Jun 2021
				Recruiting, extension study (NCT02446132)	Avanir	Dec 2015	Jun 2022
				Recruiting (NCT04464564)	Avanir	Sep 2020	Dec 2024
				Recruiting, extension study (NCT04408755)	Avanir	Jul 2020	Dec 2024
Azeliragon	Amyloid, inflammation	RAGE antagonist; to reduce Aβ transport into the brain; mitigate toxic effects of oligomers and reduce inflammation	DMT	Active, not recruiting *(NCT03980730)	vTv Therapeutics	Jun 2019	Jul 2023
Blarcamesine (ANAVEX2-73)	Synaptic plasticity/neuroprotection	Sigma-1 receptor agonist, M2 autoreceptor antagonist; to ameliorate oxidative stress, protein misfolding, mitochondrial dysfunction, and inflammation	DMT	Recruiting *(NCT03790709)	Anavex Life Sciences	Jul 2018	Dec 2021
				Recruiting *(NCT04314934)	Anavex Life Sciences	Oct 2019	Dec 2023
BPDO-1603	Undisclosed	Undisclosed	Cognitive enhancer	Recruiting (NCT04229927)	Hyundai Pharmaceutical	Feb 2020	Mar 2023
Brexpiprazole	Neurotransmitter Receptors	Atypical antipsychotic; D2 receptor partial agonist; serotonin-dopamine modulator	Neuropsychiatric symptoms agent (agitation)	Recruiting *(NCT03620981)	Otsuka	Aug 2018	Nov 2021

(Continues)

TABLE 1 (Continued)

Agent	CAD ROMechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
				Recruiting, extension study (NCT03594123)	Otsuka	Oct 2018	Jul 2022
				Recruiting (NCT03548584)	Otsuka	May 2018	Apr 2022
				Recruiting, extension study (NCT03724942)	Otsuka	Nov 2018	May 2021
Caffeine	Metabolism and bioenergetics	Pleiotropic effect on CNS function	Cognitive enhancer	Not yet recruiting (NCT04570085)	University Hospital, Lille	Nov 2020	Nov 2023
Donepezil	Neurotransmitter receptors	Acetylcholinesterase inhibitor	Cognitive enhancer	Not yet recruiting (NCT04661280)	Assistance Publique - Hôpitaux de Paris	Feb 2021	Aug 2023
Escitalopram	Neurotransmitter receptors	Selective serotonin reuptake inhibitor	Neuropsychiatric symptoms agent (agitation)	Recruiting (NCT03108846)	Johns Hopkins University, NIA	Jan 2018	Aug 2022
Gantenerumab	Amyloid	Monoclonal antibody directed at Aβ plaques and oligomers	DMT	Active, not recruiting (NCT02051608)	Roche	Mar 2014	Apr 2021
				Recruiting (NCT03444870)	Roche	Jun 2018	Nov 2023
				Active, not recruiting (NCT03443973)	Roche	Aug 2018	Nov 2023
				Recruiting, extension study (NCT04339413)	Roche	May 2020	Feb 2023
				Not yet recruiting, extension study (NCT04374253)	Roche	Feb 2021	Dec 2024
Gantenerumab & solanezumab	Amyloid	Monoclonal antibody directed at Aβ plaques and oligomers (gantenerumab); monoclonal antibody directed at Aβ monomers (solanezumab); given in separate arms of the trial	DMT	Recruiting *(NCT01760005)	Washington University, Eli Lilly, Roche, NIA, Alzheimer's Association	Dec 2012	Jul 2022
Ginkgo biloba	Metabolism and bioenergetics	Plant extract with antioxidant properties to improve mitochondrial function	Cognitive enhancer	Recruiting *(NCT03090516)	Nanjing Medical University	Aug 2016	Mar 2020
Guanfacine	Neurotransmitter receptors	Alpha-2 adrenergic agonist	Cognitive enhancer	Recruiting (NCT03116126)	Imperial College London, UK National Institute of Health Research	Jan 2019	Mar 2021

(Continues)

TABLE 1 (Continued)

Agent	CAD ROMechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
GV-971	Gut–brain axis	Algae-derived acidic oligosaccharides; changes microbiome to reduce peripheral and central inflammation	DMT	Recruiting (NCT04520412)	Shanghai Greenvalley	Oct 2020	Oct 2026
Icosapent ethyl (IPE)	Oxidative stress	Purified form of the omega-3 fatty acid EPA; to improve synaptic function and reduce inflammation	DMT	Recruiting *(NCT02719327)	VA Office of Research and Development, University of Wisconsin, Madison	Jun 2017	Nov 2021
Lecanemab (BAN2401)	Amyloid	Monoclonal antibody directed at Aβ protofibrils	DMT	Recruiting (NCT03887455)	Eisai, Biogen	Mar 2019	Aug 2024
				Recruiting (NCT04468659)	Eisai, Biogen, ACTC, NIA	Jul 2020	Oct 2027
Losartan & amlodipine & atorvastatin + exercise	Vasculature	Angiotensin II receptor blocker (losartan), calcium channel blocker (amlodipine), cholesterol agent (atorvastatin)	DMT	Active, not recruiting *(NCT02913664)	University of Texas Southwestern	Feb 2017	Mar 2022
Metformin	Metabolism and bioenergetics	Insulin sensitizer to improve CNS glucose metabolism	DMT	Not yet recruiting *(NCT04098666)	Columbia University, NIA	Jan 2021	Apr 2024
Mirtazapine	Neurotransmitter receptors	Alpha-1 antagonist	Neuropsychiatric symptoms agent (agitation)	Active, not recruiting (NCT03031184)	University of Sussex	Jan 2017	Mar 2021
Nabilone	Neurotransmitter receptors	Synthetic cannabinoid; antiemetic	Neuropsychiatric symptoms agent (agitation)	Not yet recruiting (NCT04516057)	Sunnybrook Health Sciences Center, ADDF	Oct 2020	Oct 2025
NE3107	Inflammation	MAPK-1/3 inhibitor; reduces proinflammatory NFκB activation	DMT	Not yet recruiting (NCT04669028)	Neurmedix	Apr 2021	Jan 2023
Octohydro-aminoacridin succinate	Neurotransmitter receptors	Acetylcholinesterase inhibitor	Cognitive enhancer	Recruiting (NCT03283059)	Shanghai Mental Health Center	Aug 2017	Feb 2021
Omega-3 (DHA+EPA)	Oxidative stress	Antioxidant	DMT	Recruiting (NCT03691519)	University Hospital, Toulouse	Apr 2018	Dec 2023
Solanezumab	Amyloid	Monoclonal antibody directed at Aβ monomers	DMT	Active, not recruiting (NCT02008357)	Eli Lilly, ATRI	Feb 2014	Jan 2023
Tricaprilin	Metabolism and bioenergetics	Caprylic triglyceride; to induce ketosis and improve mitochondrial and neuronal function	DMT	Not yet recruiting (NCT04187547)	Cerecin	Jan 2021	Feb 2023

(Continues)

TABLE 1 (Continued)

Agent	CAD ROMechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Troriluzole (BHV4157)	Synaptic plasticity/neuroprotection	Glutamate modulator; prodrug of riluzole; to improve synaptic function	DMT	Active, not recruiting *(NCT03605667)	Biohaven Pharma, ADCS	Jul 2018	Dec 2020
TRx0237	Tau	Tau protein aggregation inhibitor	DMT	Recruiting (NCT03446001)	TauRx Therapeutics	Jan 2018	Jun 2023

Abbreviations: ACTC, Alzheimer's Clinical Trial Consortium; ADCS, Alzheimer's Disease Cooperative Study; ADDF, Alzheimer's Drug Discovery Foundation; ATRI, Alzheimer's Therapeutic Research Institute; Aβ, amyloid beta; CADRO, Common Alzheimer's Disease and Related Disorders Research Ontology; DMT, disease-modifying therapy; EPA, eicosapentaenoic acid; GABA, gamma-aminobutyric acid; MAPK, mitogen activated protein kinase; NFκB, nuclear factor kappa B; NIA, National Institute on Aging; SSRI, selective serotonin reuptake inhibitor; SV2A, synaptic vesicle protein 2A.
Notes: Twenty-eight agents in 41 Phase 3 clinical trials currently ongoing as of January 5, 2021 according to ClinicalTrials.gov. Bolded terms represent new agents into the 2021 Phase 3 pipeline since 2020.
*Phase 2/3 trials.

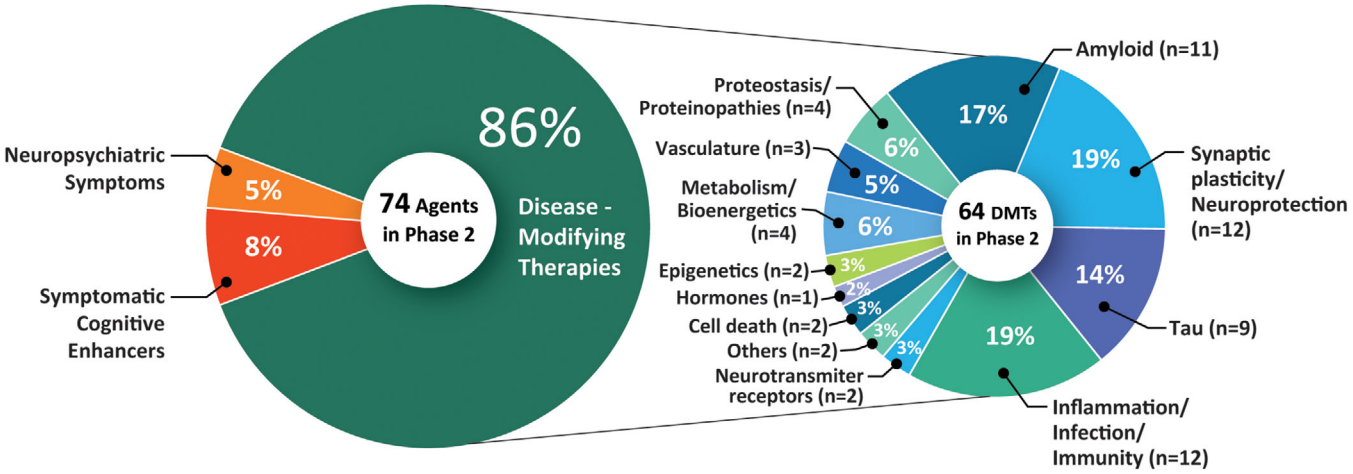

FIGURE 3 Mechanisms of action of agents in Phase 2. Figure: J Cummings; M de la Flor, PhD, Illustrator

Trials of DMTs enrolling mild-to-moderate AD dementia participants included an average of 504 participants and had a mean duration of 177 weeks (including the recruitment and the treatment period). The mean treatment exposure period was 154 weeks for prevention trials, 87 weeks for prodromal AD or prodromal AD/mild AD dementia trials, and 31 weeks for mild-to-moderate AD dementia trials. The mean duration of cognitive enhancer trials was 161 weeks (22 treatment weeks), and they included an average of 367 participants. Trials of agents for behavioral symptoms had a mean duration of 210 weeks (15 treatment weeks) and included a mean of 447 subjects. Calculated recruitment periods for trials were: prevention (172 weeks), prodromal AD and prodromal AD/mild AD dementia (120 weeks), and AD dementia trial (123 weeks). Two thirds of Phase 3 trials took longer to complete than originally planned as recorded on ClinicalTrials.gov. The time required for recruitment of the patient population typically exceeded the treatment period by up to two- to five-fold.

3.3 | Phase 2

In Phase 2 there are 74 agents in 87 trials (Figure 1, Figure 3, Table 2). Thirty (40.5%) of the Phase 2 agents are repurposed from other indications. Of Phase 2 candidate treatments, there are 64 potential DMTs, six cognitive enhancing agents, and four drugs targeting behavioral symptoms. Among DMTs in Phase 2 there are 21 biologics and 43 small molecules. Using the CADRO approach, four of the small molecules and seven of the biologics in Phase 2 have amyloid reduction as one of the mechanisms (17.2% of DMTs). Other CADRO mechanisms represented among Phase 2 DMT therapies include tau (nine agents; 14.1% of Phase 2 DMTs), inflammation/infection/immunity (12 agents; 18.8%), transmitter systems and receptors (two agents; 3.1%), oxidative stress (one agent; 1.6%), cell death (2 agents; 3.1%), proteostasis (four agents; 6.3%), metabolism and bioenergetics (four agents; 6.3%), vascular factors (three agents; 4.7%), growth factors and hormones (1 agent; 1.6%),

TABLE 2 Agents in Phase 2 of Alzheimer's disease drug development (ClinicalTrials.gov accessed January 5, 2021)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
ABvac40	Amyloid	Active immunotherapy to remove Aβ	DMT	Recruiting (NCT03461276)	Araclon Biotech	Feb 2018	Feb 2022
ACI-35	Tau	Active immunotherapy targeting tau	DMT	Recruiting *(NCT04445831)	AC Immune, Janssen	Jul 2019	Oct 2023
AD-35	Neurotransmitter receptors	Acetylcholinesterase inhibitor	Cognitive enhancer	Active, not recruiting (NCT03625401)	Zhejiang Hisun Pharmaceutical	Oct 2018	Dec 2020
				Active, not recruiting (NCT03790982)	Zhejiang Hisun Pharmaceutical	Dec 2018	Jul 2021
AL002	Inflammation	Monoclonal antibody targeting TREM2 receptors to promote microglial clearance of Aβ	DMT	Recruiting (NCT04592874)	Alector, AbbVie	Nov 2020	Aug 2023
ALZ-801	Amyloid	Prodrug of tramiprostate; inhibits Aβ aggregation into toxic oligomers	DMT	Recruiting (NCT04693520)	Alzheon	Sep 2020	May 2023
ALZT-OP1 (cromolyn + ibuprofen)	Inflammation	Combination therapy addressing microglial modulation; promoting microglial clearance of Aβ	DMT	Recruiting *(NCT04570644)	AZTherapies	Aug 2020	Dec 2020
AMX0035	Cell death	Reduce cell death associated with mitochondrial dysfunction; modulate neuroinflammation	DMT	Active, not recruiting (NCT03533257)	Amylyx Pharmaceuticals, ADDF, Alzheimer's Association	Aug 2018	Dec 2020
APH-1105	Amyloid	Alpha-secretase modulator to reduce Aβ production	DMT	Not yet recruiting (NCT03806478)	Aphios	Jun 2021	Dec 2022
AR1001	Synaptic plasticity/ neuroprotection	PDE-5 inhibitor; improve synaptic plasticity	DMT	Active, not recruiting (NCT03625622)	AriBio Co.	Apr 2019	Jan 2021
ATH-1017 (NDX-107)	Synaptic plasticity/ neuroprotection	Activates signaling via the hepatocyte growth factor system to regenerate neurons and enhance synaptic plasticity	DMT	Recruiting (NCT04488419)	Athira Pharma	Sep 2020	Oct 2022
				Recruiting (NCT04491006)	Athira Pharma	Nov 2020	Mar 2022
BCG vaccine	Inflammation/ immunity	Vaccination against tuberculosis infection; immunomodulator	DMT	Not yet recruiting (NCT04449926)	Mindful Diagnostics and Therapeutics	Nov 2020	Dec 2021
Benfotiamine	Metabolism and bioenergetics	Synthetic thiamine to improve neuronal function	DMT	Active, not recruiting (NCT02292238)	Burke Medical Research Institute, Columbia University, NIA, ADDF	Nov 2014	May 2021

(Continues)

TABLE 2 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Blarcamesine (ANAVEX 2-73)	Synaptic plasticity/ neuroprotection	Sigma-1 receptor agonist; M2 antagonist; ameliorate oxidative stress, protein misfolding, mitochondrial dysfunction and inflammation	DMT	Active, not recruiting, extension study (NCT02756858)	Anavex Life Sciences	Mar 2016	Nov 2020
BPN14770	Synaptic plasticity/ neuroprotection	PDE-4 inhibitor; prolongs cAMP activity and improves neuronal plasticity	DMT	Active, not recruiting (NCT03817684)	Tetra Discovery Partners	Apr 2019	Feb 2020
Bromocriptine	Neurotransmitter receptors	Dopamine agonist with anti-Aβ effects	DMT	Recruiting *(NCT04413344)	Kyoto University	Jun 2020	Mar 2022
Bryostatin 1	Synaptic plasticity/ neuroprotection	Protein Kinase C inhibitor; facilitates synaptogenesis	DMT	Recruiting (NCT04538066)	Neurotrope Bioscience, NIH, NIA	Aug 2020	Nov 2022
BXCL501	Neurotransmitter receptors	Sublingual dexmedetomidine; selective α2-adrenergic receptor agonist	Neuropsychiatric symptoms agent (agitation)	Recruiting (NCT04251910)	BioXcel Therapeutics	Dec 2019	Apr 2020
Crenezumab	Amyloid	Monoclonal antibody targeting soluble Aβ oligomers	DMT	Active, not recruiting (NCT01998841)	Genentech, NIA Banner Alzheimer's Institute	Dec 2013	Feb 2022
CORT108297	Hormones	Selective glucocorticoid receptor antagonist; reduce neuroendocrine stress responses	Cognitive enhancer	Recruiting (NCT04601038)	Johns Hopkins University	Feb 2021	Dec 2023
Curcumin + aerobic yoga	Inflammation	Herb with antioxidant and anti-inflammatory properties	DMT	Active, not recruiting (NCT01811381)	VA Office of Research and Development	Jan 2014	Dec 2020
Dapagliflozin	Metabolism and bioenergetics	SGLT2 inhibitor; to improve insulin sensitivity and CNS glucose metabolism	DMT	Recruiting *(NCT03801642)	University of Kansas	Jan 2019	Oct 2022
Daratumumab	Inflammation/ immunity	Monoclonal antibody targeting CD38; regulates microglial activity	DMT	Recruiting (NCT04070378)	Northwell Health, Janssen	Nov 2019	Jun 2022
Dasatinib + quercetin	Inflammation/ immunity	Tyrosine kinase inhibitor (dasatinib) and flavonoid (quercetin); senolytic therapy approach to reduce senescent cells and tau aggregation	DMT	Recruiting* (NCT04063124)	The University of Texas Health Science Center at San Antonio, Mayo Clinic	Feb 2020	Aug 2023

(Continues)

TABLE 2 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
				Not yet recruiting (NCT04685590)	Wake Forest University, The University of Texas Health Science Center at San Antonio, Mayo Clinic	Mar 2021	Mar 2031
Deferiprone	Cell death	Iron chelating agent; reduce damaging reactive oxygen species	DMT	Recruiting (NCT03234686)	Neuroscience Trials Australia	Jan 2018	Dec 2021
DHA	Oxidative stress	Omega 3 fatty acid; improve synaptic function; antioxidant	DMT	Recruiting (NCT03613844)	University of Southern California, NIA, ADDF	Jul 2018	Sep 2024
Donanemab (LY3002813)	Amyloid	Monoclonal antibody specific for pyroglutamate form of Aβ	DMT	Active, not recruiting (NCT03367403)	Eli Lilly	Dec 2017	Nov 2021
				Recruiting (NCT04437511)	Eli Lilly	Jun 2020	Apr 2024
				Recruiting (NCT04640077)	Eli Lilly	Nov 2020	Mar 2023
Dronabinol	Neurotransmitter receptors	CB1 and CB2 endocannabinoid receptor partial agonist	Neuropsychiatric symptoms agent (agitation)	Recruiting (NCT02792257)	Mclean Hospital, Johns Hopkins University	Mar 2017	May 2022
Edonerpic (T-817MA)	Synaptic plasticity/ neuroprotection	Neurotrophic agent; activates sigma receptors to preserve synaptic plasticity; protect against Aβ toxicity	DMT	Recruiting (NCT04191486)	Toyama Chemical	Dec 2019	Oct 2022
Elayta (CT1812)	Synaptic plasticity/ neuroprotection	Sigma-2 receptor antagonist; competes with oligomeric Aβ binding; protect against Aβ-induced synaptic toxicity	DMT	Active, not recruiting (NCT03507790)	Cognition Therapeutics	Oct 2018	Jul 2020
				Active, not recruiting *(NCT03493282)	Cognition Therapeutics	Apr 2018	Mar 2021
Gantenerumab	Amyloid	Monoclonal antibody directed at Aβ plaques and oligomers	DMT	Recruiting (NCT04592341)	Roche	Dec 2020	Feb 2024
GB301	Inflammation/ immunity	Regulatory T cells; reduce neuroinflammation	DMT	Not yet recruiting *(NCT03865017)	GMP BIO, BHT Lifescience Australia	Dec 2019	Dec 2021
Gosuranemab (BIIB092)	Tau	Monoclonal antibody targeting truncated form of tau	DMT	Active, not recruiting (NCT03352557)	Biogen	May 2018	Mar 2024
Grapeseed extract	Proteostasis/ proteinopathies	Polyphenolic compound; antioxidant; prevent aggregation of Aβ and tau	DMT	Active, not recruiting (NCT02033941)	Mount Sinai School of Medicine, NCCIH	Nov 2014	Dec 2021

(Continues)

TABLE 2 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
GV1001	Epigenetic	hTERT peptide vaccine; mimics extra-telomeric functions to inhibit neurotoxicity, apoptosis, and reactive oxygen species	DMT	Not yet recruiting (NCT03959553)	GemVax & Kael	Sep 2019	Feb 2022
IONIS MAPTRx (BIIB080)	Tau	Antisense oligonucleotide targeting tau expression; MAPT RNA inhibitor	DMT	Active, not recruiting *(NCT03186989)	Ionis Pharmaceuticals	Jun 2017	May 2022
IVIG (NewGam 10%)	Amyloid	Polyclonal antibody; remove amyloid	DMT	Active, not recruiting (NCT01300728)	Sutter Health	Jan 2011	Dec 2019
JNJ-63733657	Tau	Monoclonal antibody targeting soluble tau	DMT	Not yet recruiting (NCT04619420)	Janssen	Jan 2021	Mar 2025
Lamivudine (3TC)	Epigenetic	Nucleoside reverse transcriptase inhibitor; reduces genetic rearrangements	DMT	Not yet recruiting *(NCT04552795)	University of Texas Health Science Center at San Antonio	Feb 2021	Jun 2022
Lecanemab (BAN2401)	Amyloid	Monoclonal antibody directed at protofibrils	DMT	Active, not recruiting (NCT01767311)	Eisai	Dec 2012	Feb 2025
Lenalidomide	Inflammation/ immunity	Reduce inflammatory cytokines; modulate innate and adaptive immune responses	DMT	Recruiting (NCT04032626)	Cleveland Clinic, NIA	Jul 2020	Sep 2024
Levetiracetam	Synaptic plasticity/ neuroprotection	SV2A modulator; improve synaptic function; reduce Aβ-induced neuronal hyperactivity	DMT	Active, not recruiting (NCT02002819)	University of California, San Francisco	Jun 2014	Dec 2021
				Active, not recruiting (NCT03489044)	UCB Pharma, University of Oxford, NHS Foundation Trust	Oct 2018	Sep 2021
				Recruiting (NCT03461861)	Medical College of Wisconsin, NIA	Apr 2019	Mar 2021
				Recruiting (NCT03875638)	Beth Israel Deaconess Medical Center	Aug 2019	Nov 2023
Liraglutide	Metabolism and bioenergetics	Glucagon-like peptide 1 receptor agonist; improve CNS glucose metabolism	DMT	Active, not recruiting (NCT01843075)	Imperial College London	Jan 2014	Dec 2019
L-Serine	Inflammation	Dietary amino acid; reduce brain inflammation and preserve nerve cells	DMT	Recruiting (NCT03062449)	Dartmouth-Hitchcock Medical Center	Mar 2017	Dec 2021

(Continues)

TABLE 2 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Lupron (leuprolide acetate depot)	Growth factors and hormones	GnRH receptor agonist; reduce effects of elevated GnRH and gonadotropins on the brain	DMT	Recruiting (NCT03649724)	New York University	Dec 2020	Feb 2026
Metabolic cofactor supplementation	Metabolism and bioenergetics	Mixture of N-acetylcysteine, L-carnitine tartrate, nicotinamide roboside, and serine to increase mitochondrial activity	Cognitive enhancer	Recruiting (NCT04044131)	Istanbul Medipol University Hospital, ScandiBio Therapeutics	Dec 2019	Sep 2020
Montelukast	Inflammation	Cysteinyl leukotriene type 1 (cysLT-1) receptor antagonist; effects on inflammatory processes, neuronal injury, blood-brain-barrier integrity, and Aβ protein accumulation	DMT	Recruiting (NCT03402503) –buccal film	IntelGenx Corp.	Nov 2018	Jul 2021
				Recruiting (NCT03991988)—tablet	Emory University	Sep 2019	Jun 2022
Neflamapimod (VX-745)	Synaptic plasticity/ neuroprotection	p38 MAPK-α inhibitor; enhance endolysosomal function to reduce synaptic dysfunction	DMT	Recruiting (NCT03435861)	EIP Pharma	Oct 2018	Jan 2021
Nicotinamide	Tau	HDAC inhibitor; to reduce tau-induced microtubule depolymerization and tau phosphorylation	DMT	Recruiting (NCT03061474)	University of California, Irvine	Jul 2017	Jun 2020
Nicotine transdermal patch	Neurotransmitter receptors	Nicotinic acetylcholine receptor agonist	Cognitive enhancer	Recruiting (NCT02720445)	University of Southern California, NIA, ATRI, Vanderbilt University	Jan 2017	Dec 2020
Nilotinib	Proteostasis/ proteinopathies	Tyrosine kinase inhibitor; autophagy enhancer; promotes clearance of Aβ and tau	DMT	Active, not recruiting (NCT02947893)	Georgetown University	Jan 2017	Feb 2020
Omega-3 PUFA	Vasculature	Polyunsaturated fatty acid; reduce damage to small blood vessels	DMT	Active, not recruiting (NCT01953705)	Oregon Health and Science University, NIA	May 2014	Jun 2021
Pepinemab (VX15)	Inflammation	Monoclonal antibody directed at semaphorin 4D to reduce inflammation	DMT	Recruiting *(NCT04381468)	Vaccinex, ADDF, Alzheimer's Association	Sep 2020	Dec 2021

(Continues)

TABLE 2 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Posiphen	Proteostasis/ proteinopathies	Inhibitor of APP and α-synuclein	DMT	Recruiting *(NCT02925650)	QR Pharma, ADCS	Mar 2017	Dec 2020
				Recruiting *(NCT04524351)	Annovis Bio, Parexel	Aug 2020	Sep 2021
Prazosin	Neurotransmitter receptors	Alpha-1 adrenoreceptor antagonist	Neuropsychiatric symptoms agent (agitation)	Recruiting (NCT03710642)	ADCS, NIA	Oct 2018	Dec 2022
PQ912	Amyloid	Glutaminyl cyclase (QC) enzyme inhibitor to reduce pyroglutamate Aβ (pGlu-Aβ) production	DMT	Not yet recruiting (NCT03919162)	Vivoryon Therapeutics AG, ADCS, NIA	Jun 2021	Jan 2023
				Recruiting (NCT04498650)	Vivoryon Therapeutics AG, ADCS, NIA	Jul 2020	Jul 2023
PU-AD	Tau	Heat shock protein 90 inhibitor; to prevent aggregation and hyperphosphorylation of tau	DMT	Active, not recruiting (NCT04311515)	Samus Therapeutics	Jun 2020	Dec 2022
Rapamycin (sirolimus)	Proteostasis/ proteinopathies	mTOR inhibitor; ameliorate metabolic and vascular effects of aging	DMT	Not yet recruiting (NCT04629495)	The University of Texas Health Science Center at San Antonio	Jan 2021	Aug 2023
RO7126209 (brain shuttle gantenerumab)	Amyloid	Anti-Aβ monoclonal antibody with enhanced BBB penetration	DMT	Recruiting *(NCT04639050)	Roche	Mar 2021	Oct 2024
SAGE-718	Neurotransmitter receptors	NMDA receptor positive allosteric modulator	Cognitive enhancer	Not yet recruiting (NCT04602624)	Sage Therapeutics	Dec 2020	Jun 2021
Semorinemab (RO7105705)	Tau	Monoclonal antibody to remove extracellular tau	DMT	Active, not recruiting (NCT03289143)	Genentech	Oct 2017	Jun 2022
				Active, not recruiting (NCT03828747)	Genentech	Jan 2019	Jun 2023
S-equol (AUS-131)	Metabolism and bioenergetics	Agonist of non-hormonal estrogen receptor B located on mitochondria to potentiate mitochondrial function	DMT	Recruiting (NCT03101085)	Ausio Pharmaceuticals	May 2017	Nov 2020
Sovateltide (PMZ-1620)	Neurogenesis	Endothelin B receptor agonist; augments activity of neuronal progenitor cells	DMT	Recruiting (NCT04052737)	Pharmazz	Mar 2018	Aug 2021

(Continues)

TABLE 2 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Sumifilam (PTI-125)	Synaptic plasticity/ neuroprotection	Filamin A protein inhibitor; stabilize the interaction of soluble Aβ and the alpha7 nicotinic acetylcholine receptor, reducing Aβ and synaptic dysfunction	DMT	Recruiting (NCT04388254)	Cassava Sciences, NIA	Mar 2020	Apr 2022
Suvorexant	Neurotransmitter receptors	Dual orexin receptor antagonist; improved sleep with effects on CSF Aβ	DMT	Not yet recruiting (NCT04629547)	Washington University School of Medicine	Jan 2021	Jan 2025
Tacrolimus	Synaptic plasticity/ neuroprotection	Calcineurin inhibitor; to prevent Aβ-induced dendritic spine loss and synaptic dysfunction	DMT	Not yet recruiting (NCT04263519)	Massachusetts General Hospital	Dec 2021	Jan 2023
Telmisartan & Perindopril	Vasculature	Angiotensin II receptor blocker (telmisartan); angiotensin converting enzyme inhibitor (perindopril)	DMT	Recruiting (NCT02085265)	Sunnybrook Health Sciences Centre, ADDF	Mar 2014	Mar 2022
THC-free CBD oil	Neurotransmitter receptors	Cannabinoid with effects on cannabinoid receptors	Neuropsychiatric symptoms agent (agitation)	Not yet recruiting (NCT04436081)	Eastern Virginia Medical School, Ananda Hemp	Jul 2020	Dec 2021
Thiethylperaz (TEP)	Amyloid	Activates transport protein ABCC1 to remove Aβ	DMT	Active, not recruiting (NCT03417986)	Immungenetics AG	Nov 2017	Jul 2021
Tilavonemab (ABBV-8E12)	Tau	Monoclonal antibody to remove tau and prevent propagation	DMT	Active, not recruiting (NCT02880956)	AbbVie	Oct 2016	Jul 2021
				Recruiting, extension study (NCT03712787)	AbbVie	Mar 2019	Jul 2026
Vafidemstat (ORY-2001)	Synaptic plasticity/ neuroprotection	HDAC demethylase inhibitor and MAO-B inhibitor; neuroprotective	DMT	Active, not recruiting (NCT03867253)	Oryzon Genomics, ADDF	May 2019	Nov 2020
Valacyclovir	Infection/immun	Antiviral against HSV-1 and -2 infection; to prevent Aβ aggregation and plaque deposition	DMT	Recruiting (NCT03282916)	New York State Psychiatric Institute, NIH, NIA	Feb 2018	Aug 2022
VGH-AD1	Undisclosed	Traditional Chinese herbal medicine	Cognitive enhancer	Not yet recruiting (NCT04249869) *	Taipei Veterans General Hospital, Taiwan	Feb 2020	Dec 2020

(Continues)

TABLE 2 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Zagotenemab (LY3303560)	Tau	Monoclonal antibody to remove tau and reduce tau propagation	DMT	Active, not recruiting (NCT03518073)	Eli Lilly	Apr 2018	Oct 2021

Abbreviations: ADCS, Alzheimer's Disease Cooperative Study; ADDF, Alzheimer's Drug Discovery Foundation; APP, amyloid precursor protein; Aβ, amyloid beta; BBB, blood-brain barrier; CADRO, Common Alzheimer's Disease and Related Disorders Research Ontology; cAMP, cycling adenosine monophosphate; CB, cannabinoid; DMT, disease-modifying therapy; GnRH, gonadotropin-releasing hormone; HSV, herpes simplex virus; hTERT, human telomerase reverse transcriptase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NCCIH, National Center for Complementary and Integrative Health; NIA, National Institute on Aging; NMDA, N-methyl-D-aspartate; PDE, phosphodiesterase; PUFA, polyunsaturated fatty acids; SGLT2, sodium glucose transporter 2; SV2A, synaptic vesicle protein 2A; TREM2, Triggering Receptor Expressed On Myeloid Cells 2.
Notes: Seventy-four agents in 87 Phase 2 clinical trials currently ongoing as of January 5, 2021 according to ClinicalTrials.gov. Bolded terms represent new agents into the 2021 Phase 2 pipeline since 2020.
*Phase 1/2 trials.

synaptic plasticity/neuroprotection (11 agents; 17.2%), epigenetic regulators (one agent; 1.6%), and neurogenesis (one agent; 1.6%). Figure 3 shows the MOAs of agents in Phase 2. There are six trials in Phase 2 involving cell therapies (see Table 4). Twenty-six of the Phase 2 DMT agents are repurposed after approval for use in another indication. Since the 2020 review, 16 trials have been completed or terminated and there are 22 new agents in the Phase 2 pipeline.

Two Phase 2 trials are prevention trials involving participants with preclinical AD (assessing crenezumab and levetiracetam); 49 trials involved patients with prodromal or prodromal/mild AD dementia; 30 were trials for mild-to-moderate AD; one trial included patients with mild, moderate, or severe AD; one trial included preclinical patients and patients with prodromal/mild AD; and one trial was for mild-to-moderate AD or healthy participants.

Phase 2 trials for DMTs included an average of 147 participants in each trial and were on average 197 weeks in duration including an average of 52 weeks of treatment and 121 weeks for recruitment. Phase 2 trials for cognitive-enhancing agents included an average of 117 participants and were on average 103 weeks in duration including an average of 31 weeks of treatment. Phase 2 trials for agents targeting behavioral symptoms included 104 participants and were on average 145 weeks in duration including an average of 8 weeks of treatments. Of Phase 2 trials 78.6% took longer to complete than originally planned as recorded on ClinicalTrials.gov. All types of trials took between two and three times longer to recruit patients to the trial than to assess the effects of the treatment during the exposure period.

3.4 | Phase 1

Phase 1 has 24 agents in 24 trials (Figure 1, Table 3). Repurposed agents comprise 41.6% (N = 10) of the Phase 1 pipeline. Of Phase 1 candidates, there are 23 potential DMTs; one cognitive enhancing agent; and no agents targeting behavioral symptoms. There are 17 DMT small molecules and six DMT biologics being assessed in Phase 1. Review of the CADRO categories reveals that none of the small molecules and only one of the biologics in Phase I has amyloid reduction as the major mechanism attributed to the agent (4.3% of DMTs). Other CADRO mechanisms represented among Phase 1 DMT therapies include tau (one agent; 4.3% of Phase 1 DMTs), inflammation (five agents; 21.7%), cell death (one agent; 4.3%), proteostasis (two agents; 8.7%), metabolism and bioenergetics (one agent; 4.3%), vascular factors (two agents; 8.7%), growth factors and hormones (two agents; 8.7%), synaptic plasticity/neuroprotection (two agents; 8.7%), epigenetic regulators (two agents; 8.7%), circadian rhythm (one agent; 4.3%), and neurogenesis (one agent; 4.3%). There are three trials in Phase 1 involving stem cell therapies (Table 4).

Phase 1 trials have an average duration of 127 weeks (recruitment and treatment period) and include a mean of 43 participants in each trial.

3.5 | Trial sponsors

Across all trials, 49% are sponsored by the biopharma industry, 29% by academic medical centers (usually with funding from NIH), 14% are public–private partnerships, and 7% by others. In Phase 3, 61% of trials are sponsored by the biopharma industry, 20% by academic medical centers (with funding from NIH), 12% are public–private partnerships, and 7% by others. In Phase 2, 47% of trials are sponsored by the biopharma industry, 31% by academic medical centers (with NIH funding), 15% are public–private partnerships, and 7% by others. Table 5 shows the sponsor of agents in each phase of development. Repurposed agents are more likely to have academic medical centers/NIH sponsors (59%) and less likely to have industry sponsors (16%; Table 5).

3.6 | Biomarkers

Table 6 shows the biomarkers used as entry criteria or as outcome measures in current Phase 2 and Phase 3 AD clinical trials of DMTs as described on ClinicalTrials.gov; not all trial descriptions on the website note if biomarkers are included in the trial.

TABLE 3 Agents in Phase 1 of Alzheimer's disease drug development (ClinicalTrials.gov accessed January 5, 2021)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
AAV-hTERT	Epigenetic	Extending telomeres may benefit AD; reduce Aβ-induced neurotoxicity; effects on multiple cellular pathways	DMT	Recruiting (NCT04133454)	Libella Gene Therapeutics	Oct 2019	Jan 2021
AAVrh.10hAI	Epigenetic	Conversion of the apoE protein isoforms in the CSF of *APOE* ε4 homozygotes from *APOE* ε4 to *APOE* ε2-*APOE* ε4	DMT	Recruiting (NCT03634007	Cornell University	Oct 2019	Dec 2021
AL003	Inflammation	Monoclonal antibody targeting SIGLEC-3 (CD33); reactivates microglia and immune cells in the brain; improve microglial clearance of toxic proteins	DMT	Recruiting (NCT03822208)	Alector	Mar 2019	Aug 2021
Allopregnanc (Allo)	Growth factors/hormones	GABA-A receptor modulator; promote neurogenesis and reduce inflammation	DMT	Recruiting (NCT03748303	University of Southern California, University of Arizona, Alzheimer's Association	Oct 2019	Oct 2020
BEY2153	Proteostasis/ proteinopathies	Aβ and tau aggregation inhibitor; inhibits neuronal death	DMT	Recruiting (NCT04476303)	BeyondBio	Aug 2020	Oct 2021
BDPP (bioactive dietary polyphenol preparation)	Proteostasis/ proteinopathies	Prevents Aβ and tau aggregation	DMT	Recruiting (NCT02502253	Johns Hopkins University, Mount Sinai School of Medicine	Jun 2015	Jun 2021
Dabigatran	Vasculature	Direct thrombin inhibitor; reduce neurovascular damage	DMT	Not yet recruiting (NCT03752294)	University of Rhode Island, ADDF, Boehringer Ingelheim	Nov 2018	Dec 2021
Dexmedetor	Circadian rhythm	Selective α2-adrenergic receptor agonist; neuroprotection	DMT	Recruiting (NCT04205539	Neurological Associates of West Los Angeles	Apr 2019	Dec 2021
Edicotinib (JNJ-40346527)	Inflammation	CSF-1R antagonist; attenuates microglial proliferation and neurodegeneration	DMT	Not yet recruiting (NCT04121208)	Janssen, University of Oxford	Nov 2020	Dec 2021
Efavirenz	Epigenetics	NNRTI; promote cholesterol removal; enhance amyloid reduction	DMT	Recruiting (NCT03706885	Case Western Reserve University, Cleveland Medical Center, Massachusetts General Hospital	May 2018	Dec 2021

(Continues)

TABLE 3 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Elayta (CT1812)	Synaptic plasticity/ neuroprotection	Sigma-2 receptor antagonist; competes with oligomeric Aβ binding at synapse	DMT	Recruiting (NCT03522129)	Cognition Therapeutics	May 2018	Mar 2021
Empagliflozin	Metabolism and bioenergetics	SGLT2 inhibitor; improve glycemic control; enhance neuronal function	DMT	Recruiting (NCT03852901	NIA	Mar 2019	Dec 2022
Emtricitabine	Inflammation	NRTI; reduce neuroinflammation	DMT	Not yet recruiting (NCT04500847)	Butler Hospital, Alzheimer's Association, Brown University	Jan 2021	Aug 2023
Lu AF87908	Tau	Monoclonal antibody to reduce tau	DMT	Recruiting (NCT04149860	Lundbeck	Sep 2019	May 2021
LY3372993	Amyloid	Monoclonal antibody to reduce Aβ	DMT	Recruiting (NCT04451408)	Eli Lilly	Jul 2020	Feb 2022
MK-1942 + donepezil	Neurotransmitter receptors	Undisclosed (MK-1942)	Cognitive enhancer	Not yet recruiting (NCT04308304	Merck	Feb 2021	Sep 2021
MK-4334	Growth factors and hormones	Corticosteroid to reduce inflammation	DMT	Not yet recruiting (NCT03740178)	Merck	Sep 2019	Feb 2020
NNI-362	Neurogenesis	Enhance neurogenesis; activates progenitor cells	DMT	Recruiting (NCT04074837	Neuronascent, NIA	Aug 2019	Dec 2020
REM0046127	Synaptic plasticity/ neuroprotection	Regulates calcium dyshomeostasis; tau and Aβ reduction	DMT	Recruiting (NCT04672135)	reMYND, NeuroScios GmbH	Nov 2020	Oct 2021
Salsalate	Inflammation	Non-steroidal anti-inflammatory to reduce inflammation	DMT	Active, not recruiting (NCT03277573	University of California, San Francisco	Jul 2017	Jul 2021
Telmisartan	Vasculature	Angiotensin II receptor blocker	DMT	Recruiting (NCT02471833)	Emory University	Apr 2015	Oct 2021
Trehalose	Cell death	Induces autophagy and promotes clearance of aggregated proteins	DMT	Recruiting (NCT04663854	Mashhad University of Medical Sciences	Aug 2020	Aug 2022
Vorinostat	Epigenetics	Histone deacetylase (HDAC) inhibitor; enhanced synaptic plasticity	DMT	Recruiting (NCT03056495)	German Center for Neurodegenerative Diseases, University Hospital, Bonn, University of Gottingen	Sep 2017	Mar 2022
XPro1595	Inflammation	TNF inhibitor; reduce neuroinflammation	DMT	Recruiting (NCT03943264	Immune Bio, Alzheimer's Association	Nov 2019	Dec 2020

Abbreviations: AAV, adeno-associated virus; ADDF, Alzheimer's Drug Discovery Foundation; *APOE*, apolipoprotein E; Aβ, amyloid beta; CADRO, Common Alzheimer's Disease and Related Disorders Research Ontology; CSF, cerebrospinal fluid; CSF-1R, colony-stimulating factor 1 receptor; DMT, disease-modifying therapy; GABA, gamma-aminobutyric acid; hTERT, human telomerase reverse transcriptase; NIA, National Institute on Aging; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; SGLT2, sodium glucose co-transporter 2; SIGLEC-3, sialic acid-binding Ig-like lectin 3; TNF, tumor necrosis factor.

Notes: Twenty-four agents in 24 Phase 1 clinical trials currently ongoing as of January 5, 2021 according to ClinicalTrials.gov. Bolded terms represent new agents into the 2021 Phase 1 pipeline since 2020.

TABLE 4 Stem cell therapy in clinical trials for Alzheimer's disease (ClinicalTrials.gov accessed January 5, 2021)

Agent	Phase	Status (CT.gov ID)	Sponsor	Subject characteristics	Amyloid evidence at entry
Allogeneic human MSCs	1	Recruiting (NCT04040348)	University of Miami	Mild-to-moderate AD with MMSE of 20–26	Amyloid PET
Allogeneic human MSCs	1	Active, not recruiting (NCT02600130)	Longeveron	Mild-to-moderate AD with MMSE of 18–24	Amyloid PET
SNK01 (autologous natural killer cell)	1	Not yet recruiting (NCT04678453)	NKMax America	MCI or AD	Not required
Allogenic adipose MSC-Exosomes	1/2	Recruiting (NCT04388982)	Ruijin Hospital, Cellular Biomedicine Group	Mild-to-moderate AD with MMSE of 10–24	Not required
Autologous adipose-derived MSCs	1/2	Active, not recruiting (NCT04228666)	Hope Biosciences	Preclinical/MCI	Amyloid PET
CB-AC-02 (placenta derived MSCs)	1/2	Recruiting (NCT02899091)	CHABiotech Co.	Mild-to-moderate AD with MMSE of 10–26	Amyloid PET
Human umbilical cord blood-derived MSCs (NEUROSTEM)	1/2	Recruiting, extension study (NCT03172117)	Medipost	Probable AD with KMMSE of 18–26	Amyloid PET
Allogeneic human MSCs	2	Recruiting (NCT02833792)	Stemedica	Mild-to-moderate AD with MMSE of 12–24	Amyloid PET
AstroStem (autologous adipose-derived MSCs)	2	Not yet recruiting (NCT04482413)	Nature Cell Co.	Mild AD with MMSE of 20–24	CSF amyloid

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; KMMSE, Korea Mini-Mental State Examination; MMSE, Mini-Mental State Examination; MSC, mesenchymal stem cell; PET, positron emission tomography.

TABLE 5 Trial sponsor for each phase of AD drug development and the number of trials of repurposed agents supported by each entity (ClinicalTrials.gov accessed January 5, 2021)

	N of trials (%)				
Sponsor	Phase 3	Phase 2	Phase 1	All phases	Repurposed agents
Biopharma industry	25 (61%)	41 (47%)	9 (38%)	75 (49%)	9 (16%)
Academic medical centers/NIH	8 (20%)	27 (31%)	9 (38%)	49 (29%)	33 (59%)
Public–private partnerships (PPP)	5 (12%)	13 (15%)	4 (17%)	22 (14%)	5 (9%)
Others	3 (7%)	6 (7%)	2 (8%)	11 (7%)	9 (16%)

Abbreviation: NIH, National Institutes of Health.

Of the 24 Phase 3 DMT trials, four trials (17%) used amyloid positron emission tomography (PET) as an entry criterion, one (4%) used cerebrospinal fluid (CSF) amyloid, and six (25%) used either amyloid PET or CSF-amyloid. Thirteen (54%) of the Phase 3 trials did not use biomarkers for study entry. In Phase 2, 11 (14%) DMT trials used amyloid PET as an entry criterion, nine (12%) used CSF amyloid, and 11 (14%) used either amyloid PET or CSF amyloid. Two (3%) of the Phase 2 DMT trials used tau PET as an entry criterion, two (3%) used either CSF amyloid or CSF tau, and one (1%) used either amyloid PET or CSF tau. Forty (53%) of the Phase 2 trials did not require biomarker confirmation for study entry. There is one trial in Phase 3 of a cognitive enhancer trial that requires CSF amyloid or CSF tau for entry.

Of Phase 3 DMT trials, 15 (63%) use biomarkers as supportive outcomes. In Phase 2, nine DMT trials (12%) have biomarkers as primary outcomes and 29 (38%) have biomarkers as supportive outcomes. Three (13%) of the Phase 3 DMT trials include tau PET imaging as an outcome and nine (12%) of Phase 2 DMT trials include tau PET imaging as an outcome.

TABLE 6 Biomarkers as outcome measures or as entry criteria in Phase 2 and Phase 3 DMT trials (ClinicalTrials.gov accessed January 5, 2021)

	N of trials (%)	
Biomarker role in trial[a]	Phase 3 DMTs	Phase 2 DMTs
Biomarker as an outcome measure[a]		
CSF amyloid	15 (25%)	10 (48%)
CSF tau	17 (28%)	9 (43%)
FDG-PET	7 (11%)	1 (5%)
vMRI	8 (13%)	8 (38%)
Plasma amyloid	7 (11%)	2 (10%)
Plasma tau	2 (3%)	1 (5%)
Amyloid PET	5 (8%)	7 (33%)
Tau PET	4 (7%)	3 (14%)
Biomarker as an entry criterion[a]		
Amyloid PET	4 (17%)	11 (14%)
CSF amyloid	1 (4%)	9 (12%)
Amyloid PET or CSF amyloid	6 (25%)	11 (14%)
Tau PET	0	2 (3%)
CSF amyloid or CSF tau	0	2 (3%)
Amyloid PET or CSF tau	0	1 (1%)

Abbreviations: CSF, cerebrospinal fluid; DMT, disease-modifying therapy; FDG, fluorodeoxyglucose; PET, positron emission tomography; vMRI, volumetric magnetic resonance imaging.

[a]Percentages refer to the percent of trials that used any biomarker as an outcome or the percent that used biomarkers as an entry criterion.

3.7 | Trial participants

Across all currently active trials, the total number of participants needed is 38,826. Of these, 25,373 are in Phase 3 trials; 12,414 in Phase 2 trials; and 1039 in Phase 1 trials. Table 7 shows the major types of trials, the average duration of exposure for each type of trial, and the number of patients currently participating in each type of trial. This allows calculation of the total number of participant-weeks across all active trials and shows that there are 2,540,014 participant weeks of time devoted to clinical trials. This sum does not include time devoted to screening prior to randomization or the number of participant-weeks consumed in screen fails of individuals who do not progress to randomization.

TABLE 8 Global distribution of trials (ClinicalTrials.gov accessed January 5, 2021)

	No. trials (%)		
	Phase 3	Phase 2	Phase 1
North America (US & Canada)	15 (37%)	52 (60%)	15 (63%)
Non–North America	12 (29%)	18 (21%)	8 (33%)
Both	14 (34%)	17 (20%)	1 (4%)

3.8 | Global distribution of trials

Table 8 shows the distribution of trials divided into North American (United States and Canada) only, non–North American only (excluding United States and Canada), and North American and non–North American combined. Phase 2 trials are more often conducted in North America (60%) only and involve North America in 80%. Thirty-seven percent of Phase 3 trials involve North American only and 71% included North America and non–North American countries. Some Phase 1 trials conducted outside the United States may not be registered on ClinicalTrials.gov and may have gone undetected in this review. Across all phases, 54% of trials are conducted in North America only, 25% are conducted only outside North America, and 21% are conducted with both North American and non–North American sites. North America participates in 75% of all trials registered on ClinicalTrials.gov.

TABLE 7 Total person weeks contributed by participants for each type of trial (ClinicalTrials.gov accessed January 5, 2021)

Phase	Type of trial	Average duration of treatment (Weeks)	Total number of participants	Total participant weeks devoted to clinical trials
Phase 3	Prevention (preclinical AD)	154	4103	631,862
	DMT (not prevention)	82	14,150	1,160,300
	Cognitive enhancing	22	2200	48,400
	Psychotropic	15	4,920	73,800
Phase 2	DMT	52	11,181	581,412
	Cognitive enhancing	31	817	25,327
	Psychotropic	8	416	3328
Phase 1	All	15	1039	15,585
Total				2,540,014 weeks

Abbreviations: AD, Alzheimer's disease; DMT, disease-modifying therapy.

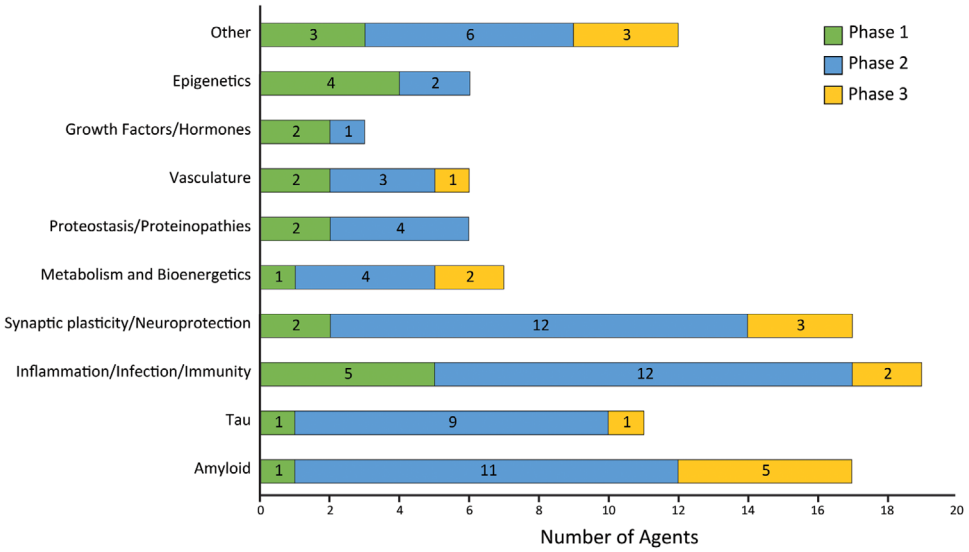

FIGURE 4 Mechanisms of action of disease-modifying agents in all phases of clinical trials grouped according to the Common Alzheimer's Disease Research Ontology (CADRO). Figure: J Cummings; M de la Flor, PhD, Illustrator

4 | DISCUSSION

In 2020, the FDA approved 53 new drugs across all therapeutic categories. Four of these were agents administered as part of imaging procedures including flortaucipir (Tauvid) to be used with PET imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment who are being evaluated for AD. Eleven of the approved treatments addressed central nervous system (CNS) diseases.[21] Five of the approved agents are DMTs involving neurodegeneration—2 for neuromyelitis optica, 1 for multiple sclerosis, 1 for Duchenne muscular dystrophy, and 1 for spinal muscular atrophy. Treatments for neuroblastoma, neurofibromatosis, migraine, on/off in Parkinson's disease, and an agent for sedation comprised the other CNS approvals. There were no new therapies for AD. Thirty-six percent of the CNS approvals were for DMTs, suggesting that DMT-related targets, biomarkers, and trial designs are progressing.

The AD drug development pipeline comprises 126 agents in 152 trials (Figure 1). There are 28 agents in Phase 3, 74 in Phase 2, and 24 in Phase 1. One hundred four putative DMTs are being assessed (17 in Phase 3, 64 in Phase 2, 23 in Phase 1). DMTs represent 83% of the pipeline of agents. There are 13 cognitive enhancers and nine drugs targeting neuropsychiatric symptoms in the pipeline. The 126 agents in the pipeline compares to 121 in the pipeline in 2020;[13] with one less agent in Phase 3, nine additional agents in Phase 2, and three less agents in Phase 1. Since the 2020 pipeline, 7 trials in Phase 3, 18 trials in Phase 2, and 9 trials in Phase 1 have been either completed, terminated, suspended, or the status is unknown. There are five prevention trials in Phase 3 and two prevention trials in Phase 2; the number of prevention trials in Phase 3 has remained constant over the past 6 years, while the number of Phase 2 prevention trials has varied (0 to 4).

Using the CADRO classification, review of the pipeline reveals a proliferation of mechanistic approaches to the treatment of AD (Figure 4). Phase 2 has both more agents in trials and a greater diversity of targets than other phases; this may reflect a more diversified approach to treatment targets in Phase 2 or a reduction of targets in Phase 3 because of the lack of success in Phase 2 outcomes. Amyloid and tau protein are important targets; inflammation, synaptic plasticity, neuroprotection, and bioenergetics/metabolism account for most of the rest of the current pipeline of agents.

Biomarkers play an increasing role in drug development and use the amyloid (A), tau (T), neurodegeneration (N)—A/T/N—biomarker framework.[22,23] Biomarkers are integrated into development programs for diagnostic confirmation (e.g., amyloid PET, CSF amyloid), analytic stratification (e.g., apolipoprotein E genotype), prognostic anticipation (e.g., tau PET, CSF phosphorylated tau [p-tau]), assessment of neuroprotection and disease modification (magnetic resonance imaging, fluorodeoxyglucose [FDG] PET, CSF total tau, neurofilament light [NfL], neurogranin), or for safety monitoring in monoclonal antibodies and possibly other therapies.[22] Biomarkers are rarely used for diagnostic confirmation in trials for cognitive enhancing agents or drugs targeting neuropsychiatric symptoms. Lack of diagnostic precision in these trials may contribute to commonly observed challenges including robust placebo responses and failure of placebo groups to decline.[24,25] More use of biologic confirmation in AD trials or more trials in populations of "dementia" including several major types of dementia and less emphasis on precise definition are anticipated. The pimavanserin trial of dementia-related psychosis is an example of the latter with five types of clinically defined dementia included in the trial population.[26]

The rapid evolution of blood-based biomarkers may have a significant impact on patient screening and diagnosis and is expected to eventually act as entry criteria or outcomes in some

circumstances. Plasma amyloid beta protein (Aβ) 42/40 correlates highly with amyloid PET[27] and is commercially available for clinical application (PrecivityAD). Plasma p-tau-181 and plasma p-tau 217 are elevated as AD advances and may be useful in trials to assess impact on tau pathology of trial participants.[28,29] Plasma NfL, a measure of neuronal degeneration, is increasingly elevated as AD progresses.[30] With these measures it is possible to characterize all of the ATN framework elements using peripheral markers. Data will soon be available regarding whether these measures can qualify participants for trials or will serve as screens indicating which participants should be further characterized by amyloid or tau PET or CSF measures.

Examination of sponsorship shows that most Phase 3 trials are supported by biopharmaceutical companies, whereas at Phase 2 47% of trials have biopharmaceutical sponsors: 31% are NIH/academic medical center trials, 15% are public–private partnerships, and 7% have other sponsors. This reflects the increased focus of biopharmaceutical companies on late-stage development and outsourcing larger portions of the early-stage drug development enterprise.[31] Repurposed agents are more common in trials in Phase 2 and more likely to be in trials sponsored by NIH/academic medical centers (Table 5). Repurposed agents rarely progress to Phase 3; the Phase 2 trials of these drugs produce invaluable data on molecules that can be reengineered to have better intellectual property protection, pathways, and processes that may be promising therapeutic targets, and effects on biomarkers or novel clinical outcomes. These trials provide important educational opportunities for a variety of trainees who will comprise the clinical trial workforce of the future.[32]

The total number of participants in trials and the total number of trial weeks they contribute is dramatic. Participants required for currently active trials total 38,826; when calculated in terms of participant-weeks in trials (Table 7), the total number in all ongoing trials is 2,540,014. There are at least an equivalent number of weeks contributed by research partners, doubling the total participant-partner weeks to 5,080,028 weeks. This large number is a marked underestimate of total weeks because it does not include weeks spent in screening prior to randomization or weeks contributed by participants who are excluded during the screening period.

A continuing challenge to trial conduct is the slow rate of recruitment. The average length of time required for recruitment of participants exceeds the duration of the treatment period in nearly all trials. There has been no trend toward shortening recruitment times over the past 5 years despite expanded efforts to improve recruitment. Although sponsors plan for slow recruitment, 66.7% of Phase 3 trials and 78.6% of Phase 2 trials took longer to complete than originally anticipated as recorded on ClinicalTrials.gov. The COVID-19 pandemic further exacerbated recruitment struggles with many clinics suspending research at least temporarily, delaying visits during this time, and experiencing attrition due to SARS-CoV-2 infections in patients and family members or an unwillingness to attend medical facilities.[33] These observations identify a gap in the trial system that requires remedy to accelerate trials and drug development.

Many trials are conducted globally to increase the number of sites and accelerate recruitment. This is especially important for large Phase 3 trials. Global trials allow diversified participant exposures and improved understanding of effects of ethnicity, standard of care, body size, nutrition, and educational level on trial outcomes. Table 8 shows that most trials conducted have US representation either as the sole country in which the trials are conducted or as part of a world-wide global trial program. This is, in part, a reflection of the fact that ClinicalTrials.gov is a US trial registry (although note that most trials conducted by sponsors anywhere in the world are registered on ClinicalTrials.gov). Combined with the participant weeks in trials noted above, it is evident that participants and research partners throughout the world are making a remarkable contribution to AD drug development efforts through trial participation.

Next generation biotherapeutics (NGBs) include cell, gene, and nucleotide therapies.[34] There are nine trials of cell therapies in AD (Table 4), one oligonucleotide targeting tau expression, and several epigenetic modulators. Technologies have advanced to facilitate trials of gene therapy in AD and trials are anticipated in the pipeline.[35] Stem cell interventions may promote nerve cell regeneration, adding a dimension to therapeutic response beyond the slowing of cognitive decline targeted by DMTs in current trials.[36,37]

Therapeutic concepts related to the larger universe of diseases of aging are beginning to influence the AD pipeline. Cell senescence occurs throughout the lifespan but plays a larger role with aging and is postulated to contribute to many diseases of aging including vascular disease, arthritis, and neurodegeneration.[38] Senolytic therapies directed at removing senescent cells are included in the AD pipeline. Three senolytics in current AD trials are metformin, rapamycin, and dasatinib plus quercetin; these therapies have shown benefit in nonclinical models of aging and AD.[39–41] A toolkit of biomarkers relevant to trials of senolytics suggests measures relevant to peripheral effects of treatment that may be useful in some AD trials.[42] Many questions remain unresolved concerning the relationship of cellular senescence and neurodegeneration/AD;[43] trials of senolytics will provide key insights into the value of these agents as treatments for AD and late-life cognitive decline.

5 | SUMMARY

Clinical trials are the sole means by which new treatments for AD can be approved. Increasing the number of trials, enhancing trial efficiency, and improving trial success are critical to advancing new therapeutics for AD. Trials are being conducted in preclinical, prodromal, and AD dementia populations in an effort to prevent, delay the onset, slow the progression, or improve the cognitive and behavioral symptoms of AD. There are slightly more agents in the AD pipeline in 2021 compared to 2020. There is an increasing diversity of targets and corresponding therapeutic mechanisms of drugs in the AD pipeline. Participants are making a remarkable contribution of 2,540,014 participant-weeks to support AD drug development, making a major contribution to treatment development efforts.

CONFLICTS OF INTEREST

JC has provided consultation to Acadia, Alkahest, AriBio, Avanir, Axsome, Behren Therapeutics, Biogen, Cassava, Cerecin, Cerevel, Cortexyme, EIP Pharma, Eisai, Foresight, GemVax, Genentech, Green Valley, Grifols, Janssen, Jazz, Merck, Novo Nordisk, Otsuka, ReMYND, Resverlogix, Roche, Signant Health, Sunovion, Suven, United Neuroscience, and Unlearn AI pharmaceutical and assessment companies. Dr. Cummings has stock options in ADAMAS, AnnovisBio, MedAvante, BiOasis, and United Neuroscience. Dr. Cummings owns the copyright of the Neuropsychiatric Inventory. Dr Cummings is supported by NIGMS grant P20GM109025; NINDS grant U01NS093334; NIA grant R01AG053798; and NIA grant P20AG068053. GL is a full-time employee of Biogen. KZ provides consultation to Green Valley Pharmaceuticals. JF has no disclosures. KT has no disclosures.

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