Received: 2 February 2021 | Revised: 12 April 2021 | Accepted: 20 April 2021 | Published online: 20 May 2021

DOI: 10.1002/trc2.12185

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

Who funds Alzheimer's disease drug development?

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Abstract

Introduction: Despite the increase in Alzheimer's disease (AD) cases in the United States, no new treatments have been approved in the United States since 2003. The costs associated with drug development programs are high and serve as a significant deterrent to AD therapeutic investigations. In this study, we analyze the sponsorship data for AD clinical trials conducted since 2016 to assess the fiscal support for AD clinical trials.

Methods: We analyzed the funding sources of all AD trials over the past 5 years as reported on ClinicalTrials.gov.

Results: There were 136 trials being conducted for treatments in the US AD therapeutic pipeline on the index date of this study. Among non-prevention trials, disease-modifying therapies (DMT) in Phase 3 were almost entirely sponsored by the biopharmaceutical industry; Phase 2 DMT trials were split between the biopharmaceutical industry and funding from the National Institutes of Health (NIH) to academic medical centers (AMCs). The majority of prevention trials received sponsorship from public–private partnerships (PPP). Trials of symptomatic agents are equally likely to have biopharmaceutical or NIH/AMC sponsorship. Most trials with repurposed agents had NIH/AMC funding (89%). Since 2016, there has been consistent growth in the number of trials sponsored both in part and fully by NIH/AMC sources and in PPP, and there has been a reduction in biopharmaceutical company–sponsored trials.

Discussion: The number of trials supported by the biopharmaceutical industry has decreased over the past 5 years; trials supported from federal sources and PPP have increased. Repurposed compounds are mostly in Phase 2 trials and provide critical mechanistic information.

KEYWORDS
Alzheimer's disease, biopharmaceutical industry, clinical trials, cognitive-enhancing agents, disease-modifying therapies, funding, National Institute on Aging, repurposing

1 | WHO FUNDS ALZHEIMER'S DISEASE DRUG DEVELOPMENT?

There are currently 5.8 million individuals with Alzheimer's disease (AD) dementia in the United States and the number is projected to increase to nearly 14 million by 2050; there will be a concomitant increase in cost from the current $290 billion annually to >$1 trillion annually if means of preventing, delaying the onset, slowing the progression, or improving the symptoms of AD are not found.[1]

AD drug development represents an urgent unmet need; there has been no new drug approval in the United States since 2003 and only one agent has been approved globally in that period.[2,3] An important disincentive to engage in AD drug development is the high cost of development programs. A 2014 analysis showed that the "out-of-pocket" cost of AD drug development including Phases 1, 2, and 3 is $413 million.[4] When the cost of failures and the cost of capitalization of the funds are included, the total cost is $5.7 billion per drug.[4] There are many organizations that support AD drug development including the National Institutes of Health (NIH), clinical trials funded by philanthropies such as the Alzheimer's Drug Discovery Foundation (ADDF), support for trials from the Alzheimer's Association (e.g., Part the Cloud initiative), and biotechnology and pharmacology companies.[5] Increasingly, trials include public–private partnerships (PPPs) involving the NIH and biopharmaceutical companies to allow more trials to be conducted while distributing the cost and risk.[6]

To better understand the funding landscape for AD clinical trials, we interrogated our database of information from ClinicalTrials.gov and our annual reviews published over the past 5 years[3,7–10] to determine what agencies and companies were involved in funding current AD clinical trials. Our goal was to define the sources of funding, to enhance the dialogue regarding how trials are funded, and to investigate how funding can be amplified to accelerate treatment development. We also sought to determine whether the funding source influenced the characteristics of trials conducted.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the sponsorship data and trial analytics for all agents assessed in clinical trials for Alzheimer's disease (AD) between 2016 and 2020 as reported in the US government database ClinicalTrials.gov.
2. **Interpretation**: Most treatments in Phase 3 and capable of becoming new therapies for AD are sponsored by the biopharmaceutical industry. Phase 2 trials may be sponsored by industry, academic centers with National Institutes of Health (NIH) funding, or by public–private partnerships (PPP). There are many repurposed agents in academic/NIH-sponsored trials. Repurposed agents are not common in Phase 3. In the past 5 years, industry-only trials have declined in number while PPP and academic/NIH trials have increased.
3. **Future directions**: Innovation in sponsoring and funding AD drug development is required. Orphan drug–type legislation, support for PPP, and identification of new means of risk reduction and cost sharing will incentivize more sponsors to engage in AD therapeutic development.

2 | METHODS

Our study is based on the clinical trial activity as reported on ClinicalTrials.gov, a comprehensive data repository of US trial activity. Trials conducted in the United States are required by law to be registered with the database within 21 days of the first participant's enrollment.[11,12] A high rate of compliance is well documented.[11–14] Most non-US trials are registered on ClinicalTrials.gov, with the majority of Phase 2 (86%) and Phase 3 (90%) trials conducted worldwide as listed in the World Health Organization trial registry represented in the US governmental database.[15]

Trial information pertinent to this study included a study's beginning date, projected end date, primary completion date, actual end date (trials with completed status), calculated trial duration, duration of treatment exposure, number of participants planned for enrollment, number of study arms, biomarker usage in study, whether a drug was approved for another indication and being tested as a repurposed therapy for AD, and sponsorship. We include all trials involving agents in Phases 1, 1/2, 2, 2/3, and 3 that were registered on ClinicalTrials.gov as of the index date of February 27, 2020. For purposes of this study, we classified Phase 1/2 as Phase 2 and Phase 2/3 as Phase 3. Trials that were designated on ClinicalTrials.gov as recruiting, active but not recruiting, enrolling by invitation, and not yet recruiting were analyzed. Trials involving stem cell therapies were not included among the agents reviewed. Our focus on funding required that we focus on US trials where funding sources are identified; the trials conducted exclusively outside of the United States were excluded from the analysis. Obtaining informed consent was not necessary in this study.

Our focus on trial funding is based on sponsorship information as reported on ClinicalTrials.gov. The governmental database labels a study's funder type by industry (i.e., biopharmaceutical companies), NIH, US federal agency, an "all others" category (individual sponsorships, academic medical centers [AMCs], consortiums, philanthropic organizations), or a combination of these sponsors. For the purposes of our study, we classify trials into four sponsorship categories: biopharmaceutical-only sponsored studies; trials funded solely from AMC or NIH sources (including philanthropy and advocacy funding); PPP trials involving sponsorships from industry in conjunction with AMC, NIH, consortium, and/or philanthropic organizations; and "other" studies not included in the defined categories.

We reviewed repurposed drugs that are Food and Drug Administration (FDA)-approved for non-AD indications as part of this study. An agent's repurposing status was determined using the information recorded on Drugs@FDA (fda.gov/drugsatfda), a governmental database containing drugs with an FDA-approved indication. The database is updated daily and has drug products that have been approved since 1939.[16]

Trials were grouped into those assessing efficacy as putative disease-modifying therapies (DMTs), trials of cognitive-enhancing agents aimed at improving cognition above baseline, and trials of drugs intended to reduce neuropsychiatric symptoms. An agent was classified as a DMT when the goal of the treatment in the trial was to delay the onset or slow the progression of the disease by modifying

TABLE 1 Trial characteristics for disease-modifying agents by funding entity (Phase 2 and Phase 3 excluding prevention trials)

	AMC/NIH	Biopharma	PPP	Other
Phase 3				
Number of trials	0	11	3	0
Mean trial duration (weeks)		283	173	
Mean treatment duration (weeks)		79	77	
Mean number of participants per arm		416	258	
Require diagnostic confirmation with amyloid biomarkers		7 of 11	1 of 3	
Phase 2				
Number of trials	21	19	9	1
Mean trial duration (weeks)	238	177	115	323
Mean treatment duration (weeks)	41	53	27	52
Mean number of participants per arm	32	109	39	20
Require diagnostic confirmation with amyloid biomarkers	8 of 21	9 of 19	6 of 9	0 of 1

Abbreviations: AMC, academic medical center; DMT, disease-modifying therapy; NIH, National Institutes of Health; PPP, public–private partnership (comprised of a biopharmaceutical company partnered with NIH, AMC, consortium, and/or philanthropic organization).

the underlying biology of AD. Some interventions may have both DMT and symptom-reducing properties; we assigned the mechanism of an agent based on the design and primary outcome measures of the trial. We separated prevention trials of DMTs involving asymptomatic at-risk individuals from treatment trials involving prodromal AD and AD dementia; the characteristics and funding of these two types of trial differ.

3 | RESULTS

There were 136 active trials on the index date of this review (February 27, 2020). This includes 110 trials of DMTs, 15 trials of drugs seeking to reduce neuropsychiatric symptoms, and 11 trials of drugs targeting cognitive enhancement. Within this dataset we analyzed all trials that included US participation.

3.1 | Trials of disease-modifying agents (excluding prevention trials)

Excluding prevention trials, there are 14 trials of DMTs in Phase 3 and 50 trials of DMTs in Phase 2. Table 1 shows trials sponsored by the four drug development funding enterprises assessed and summarizes the length of trials (including the length of time for recruitment plus the duration of treatment), duration of the drug treatment in the trial, number of participants, and whether biomarkers of AD pathology were used to define the participants included in the trial.

One hundred percent of Phase 3 DMT trials have industry participation and 11 of 14 are sponsored solely by biopharmaceutical companies. Compared to trials sponsored by PPPs, Phase 3 trials with biopharmaceutical companies as the sole sponsor take longer to recruit (the total trial time – the treatment time = 204 weeks for pharmaceutical trials and 96 weeks for the PPP trials), are larger in number of participants (416 vs. 258 per arm) and have a somewhat shorter drug treatment period (79 vs. 77 weeks).

Sponsorship of Phase 2 trials is more heterogeneous. In this phase of drug development there are many more AMC/NIH trials (21 in Phase 2 vs. 0 in Phase 3), and somewhat more trials in each of the other sponsor categories (19 biopharmaceutical in Phase 2, twelve in Phase 3; nine PPP in Phase 2, three in Phase 3; one "other" in Phase 2, zero in Phase 3). Recruitment periods for all sponsors vary from 197 weeks (AMC/NIH sponsors), 124 weeks (biopharmaceutical sponsors), 85 weeks (PPP sponsors), to 271 weeks ("other" sponsors). Treatment periods are shorter in Phase 2 than in Phase 3. Treatment periods are 41 and 53 weeks for AMC/NIH and biopharmaceutical sponsors, respectively, 27 weeks for PPP, and 52 weeks for "other" trials. The number of participants in Phase 2 trials is generally smaller than in Phase 3 trials. Biopharmaceutical trials tend to be larger (109 participants per arm) than AMC/NIH trials (32 participants per arm), PPP (39 participants per arm), or "other" (20 participants per arm). Approximately 46% of current Phase 2 trials require biomarker confirmation of amyloid abnormalities for study participation (8/21 AMC/NIH trials, 9/19 biopharmaceutical company trials, 6/9 PPP trials, and 0/1 "other" trials).

3.2 | Prevention trials

On the index date there were seven trials involving cognitively normal preclinical participants and examining prevention or delay of symptomatic AD in the 2020 pipeline. Prevention trials tend to be larger and longer than DMT non-prevention treatment trials. Most prevention trials in Phase 3 (3 of 5) are sponsored by the PPPs and have a recruitment period of 216 weeks, treatment duration of 236 weeks, and 273 participants per treatment arm. The remaining two trials are sponsored by AMC/NIH (1 trial) and "other" funding sources (1 trial); these trials have shorter respective recruitment periods (183 and 156 weeks), shorter

TABLE 2 Trial characteristics for symptomatic agents by funding entity

	AMC/NIH	Biopharma	PPP	Other
Cognitive enhancers				
Phase 3	2	2	0	0
Phase 2	3	2	1	1
Neuropsychiatric agents				
Phase 3	4	7	0	0
Phase 2	3	1	0	0

Abbreviations: AMC, academic medical center; NIH, National Institutes of Health; PPP, public–private partnership (comprised of a biopharmaceutical company partnered with NIH, AMC, consortium, and/or philanthropic organization).

treatment durations (104 and 78 weeks), and are smaller (128 and 75 participants) than those sponsored by PPPs. One prevention trial is in Phase 2 and funded by AMC/NIH. The small number of Phase 2 trials precludes further analysis.

3.3 | Trials of symptomatic agents

There are 15 trials in Phase 3 and 10 trials in Phase 2 investigating symptomatic agents. Table 2 summarizes sponsorship information, trial statistics, and AD biomarker data for trials that involve cognitive-enhancing agents and neuropsychiatric symptom reduction.

Funding categories for trials of cognitive enhancers vary: two biopharmaceutical-sponsored trials in Phase 3, two in Phase 2; twenty AMC/NIH in Phase 3, two in Phase 2; zero PPP in Phase 3, one in Phase 2; and zero "other" in Phase 3, one in Phase 2. There are too few trials for further analysis.

Sponsorship of trials in Phase 3 with agents addressing behavioral and neuropsychiatric symptoms were slightly more likely to be sponsored by biopharmaceutical companies compared to AMC/NIH (7 vs. 4). On the other hand, Phase 2 trial sponsors by AMC/NIH were marginally higher than by biopharma (3 vs. 1). There are currently no trials of neuropsychiatric agents sponsored by PPP or "other" entities. AMC/NIH trials in Phase 3 were comparable to those in Phase 2, with slightly shorter recruitment times (204 vs. 213 weeks), shorter treatment durations (13 vs. 9 weeks), and a larger number of participants (107 vs. 71 participants). Phase 3 biopharmaceutical-sponsored trials were comparatively shorter in recruitment (179 weeks), longer in treatment duration (17 weeks), and larger overall (242 participants). PPP and "other" sponsorship categories are not represented in the current pipeline. There were no neuropsychiatric agent trials in Phase 3 or Phase 2 that require amyloid-related biomarkers for study participation.

3.4 | Trials with repurposed disease-modifying agents

There are 36 trials of repurposed agents with disease-modifying objectives in the current pipeline. Only five of these are in Phase 3 trials (one from biopharmaceutical companies; one from AMC/NIH sponsors; two from PPP trials sponsors; and one "other"). The number is too small for further analysis.

In Phase 2 there are 22 trials of repurposed DMTs. Eighteen of these are sponsored by AMC/NIH and three by PPP. Ninety-five percent of trials of repurposed agents have AMC/NIH as the sole or a major sponsor. Further analysis of the 18 trials sponsored solely by AMC/NIH reveals that recruitment requires 191 weeks for a trial with 36 weeks of treatment exposure and there is a mean of 34 participants per arm.

Repurposing trials of symptomatic agents comprise two cognitive enhancers (one in Phase 3, one in Phase 2) and eight addressing behavioral symptoms (five in Phase 3, three in Phase 2).

3.5 | Trial sponsor trends from 2016 to 2020

Using the data from our annual reviews,[3,7–10] we assessed the trends in trial sponsorship over the past 5 years (Table 3). There has been a consistent increase in the number of AMC/NIH trials over the observation period (from 27 in 2016 to 48 in 2020). Likewise, there has been a steady increase of PPP trials (from 7 in 2016 to 22 in 2020). Trials sponsored solely by biopharmaceutical companies have declined (by 16% from 2016, although there is variability in the number of biopharmaceutical-sponsored trials and some years have had increases).

When trials for DMTs are examined, there has been an 89% increase in DMT trials sponsored by AMC/NIH; a 2% decrease in DMT trials sponsored by the biopharmaceutical industry; a three-fold increase in DMT trials from PPP sponsors; and no change in the number of DMT trials sponsored by other entities (3 to 4 per year).

For cognitive enhancer and neuropsychiatric trials, respectively, there was an overall decrease in funding by biopharmaceutical companies (67% and 20%) and an increase in AMC/NIH (25% and 250%). For PPP trials, there is currently one cognitive-enhancing trial and none investigating behavioral or neuropsychiatric symptoms. Only one cognitive-enhancing trial is sponsored by "other" entities.

For repurposed agents, there has been a three-fold increase in AMC/NIH-sponsored trials (from 9 in 2016 to 29 in 2020) and a seven-fold increase in PPP trials (from one in 2016 to seven in 2020). Trials of repurposed drugs sponsored by biopharmaceutical companies and other entities have remained constant (3 to 4 and 2 to 3 each year, respectively).

4 | DISCUSSION

Drug development for AD is costly and frequently ends in failure.[2,4,5] As a result, several major pharmaceutical companies have downsized or terminated their AD drug development programs, reducing investment in development of drugs for central nervous system diseases in general and treatments for AD in particular.[17–19] Funding is critical to advancing new therapies through clinical trials and our assessment of the sponsorship for trials is an attempt to better understand the recent trends and current status of funding AD trials.

TABLE 3 Trial sponsorship for Alzheimer's disease trials over the past 5 years

	AMC/NIH	Biopharma	PPP	Other
All trials				
2016	27	74	7	3
2017	31	83	12	3
2018	35	67	16	4
2019	48	83	24	4
2020	48	62	22	4
Trials of DMTs				
2016	19	51	7	3
2017	21	58	12	3
2018	23	49	13	3
2019	34	64	21	4
2020	36	50	21	3
Trials of cognitive enhancers				
2016	4	12	0	0
2017	4	10	0	0
2018	5	9	3	1
2019	6	8	2	0
2020	5	4	1	1
Trials of neuropsychiatric agents				
2016	2	10	0	0
2017	4	14	0	0
2018	6	9	0	0
2019	8	11	1	0
2020	7	8	0	0
Trials of repurposed agents				
2016	9	3	1	2
2017	10	3	1	2
2018	15	2	0	3
2019	24	2	5	3
2020	29	4	7	2

Abbreviations: AMC, academic medical center; DMT, disease-modifying therapy; NIH, National Institutes of Health; PPP, public–private partnership (comprised of a biopharmaceutical company partnered with NIH, AMC, consortium, and/or philanthropic organization).

Increased funding of trials by NIH through grants to AMCs has increased the number of trials conducted by AMCs/NIH by 78% in the past 5 years reflecting the programs of the National Institute on Aging (NIA), Alzheimer's Association, and ADDF that fund investigator-initiated trials. PPP, although still relatively few in number, have increased 214% and have become a common collaborative mechanism for drug development. PPP are a means of leveraging resources, spreading the cost, and managing the risk of drug development across several sponsors and have become important financial and scientific vehicles for drug development across therapeutic areas.[20–23] The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), the Alzheimer's Prevention Initiative (API), and the European Prevention of Alzheimer's Dementia (EPAD) program are examples of PPP for AD drug development.[24–26]

Over the course of the 5-year observation period, the number of clinical trials sponsored solely by biopharmaceutical companies (not in the context of PPP) has decreased; the number of trials funded by biopharmaceutical companies for DMTs has stayed approximately stable. This suggests that despite improved knowledge regarding how to identify distinct AD trial populations (e.g., preclinical AD, prodromal AD, AD dementia participants), better biomarkers, more well-defined biological targets, and improved ability to conduct trials,[27,28] the pharmaceutical industry is not increasing their involvement in AD trials and drug development except through the PPP mechanism.

The funding source influences the type of drug candidates chosen for clinical trials. The pharmaceutical industry sponsors primarily trials of new molecular entities (NMEs); 10 of 11 Phase 3 DMT trials and 18 of 19 Phase 2 DMT trials test NMEs. The candidates differ dramatically

in AMC/NIH trials, of which 18 of 22 Phase 2 DMT trials assess efficacy of repurposed agents and the only Phase 3 DMT trial sponsored by an AMC/NIH is a repurposed agent in a trial for AD prevention. Although we do not have data on cost of trials, the availability of inexpensive generic repurposed agents may make them more attractive and available to academic investigators supported by NIH, Alzheimer's Association, ADDF, and other funding agencies supporting academic trial initiatives. The limited patent and intellectual property opportunities for repurposed agents make them less attractive candidates for development by biopharmaceutical companies whose business model requires a substantial return on investment.

AMC/NIH-sponsored trials differ from biopharmaceutical trials in tending to be smaller in terms of participants per arm in the trial and shorter in terms of duration of exposure (Table 1). These differences may reflect the more limited funding available through AMC/NIH sources.

This analysis suggests that repurposed agents are rarely advanced to Phase 3 and that key contributions of trials of repurposed agents are to assess efficacy of agents that might be reengineered to be unique NMEs, explore the utility of modulating promising pathways in proof-of-concept trials, explore new biomarkers and trial designs to assess their trial-readiness, build trial infrastructure, and provide critical learning experiences for academic trialists.[29–31] The diversity of therapeutic targets represented by Phase 2 DMT trials provides critical foundational information for exploring new treatment targets.[32] Trials can be designed for these goals rather than anticipating their role as a Phase 2/3 contribution in a regulatory approval–type development program.

Trials sponsored by AMCs and funded by NIH or other trial funding agencies such as the Alzheimer's Association or the ADDF advance very few DMTs to Phase 3 (one in Phase 3 currently). AMCs, however, are currently conducting as many trials of cognitive enhancers as biopharmaceutical companies (five trials supported by AMCs/NIH; four trials supported by biopharmaceutical companies). AMCs are also active in developing agents addressing neuropsychiatric symptoms sponsoring four such trials in Phase 3 and three in Phase 2, compared to biopharmaceutical sponsorship of seven trials in Phase 3 and one trial in Phase 2. These observations suggest that the major opportunity for AMCs (with NIH or other non-biopharmaceutical support) to advance an agent to Phase 3 and possibly to FDA approval is in the area of symptomatic therapies.

This study has limitation including its dependence on ClinicalTrials.gov as the sole source of information on trials' this registry is comprehensive for trials conducted in the United States, the focus of the study. The absence of cost information is a limitation, as incorporating the magnitude of investment may have provided further insight into the relationship of funding to trial-related decisions. We had 5 years of data to review; longer observation periods may have yielded additional information.

This study of funding for clinical trials in AD provides the foundation for recommendations for how best to increase the number and value of AD trials. AMC/NIH-funded trials are increasing, and that trend should be sustained and championed. PPP are growing in number and offer advantages to all collaborators including biopharmaceutical enterprises and AMC/NIH; these collaborations should be supported and expanded. Biopharmaceutical trials are stable or decreasing in number and incentives such as those made available for development of drugs for orphan diseases are needed to encourage companies to commit to this therapeutic area.[33–35] Despite the sizable upfront costs, therapeutic market valuation models have found the impact of costs to be small compared to potential returns; increased awareness of this fact may serve to incentivize biopharmaceutical participation.[32] Repurposed agents have a key role in proof-of-concept/experimental medicine–type trials, and these can be designed to enhance understanding of target pathways, biomarkers, and trial designs. Success in clinical and biomarker-informed efficacy will attract biopharmaceutical partnering and venture capital and other types of investment.[36] An agenda aimed at improved trial funding is important to bring more treatments to patients more quickly.

CONFLICT OF INTERESTS

Dr. Cummings has provided consultation to Acadia, Alkahest, Annovis, Avanir, Axsome, Biogen, Cassava, Cerecin, Cognoptix, Cortexyme, EIP Pharma, Eisai, Green Valley, Grifols, Jazz, Karuna, Otsuka, ReMYND, Resverlogix, Roche, Signant Health, Sunovion, Suven, United Neuroscience, and Unlearn AI pharmaceutical and assessment companies. Dr. Cummings has stock options in ADAMAS, MedAvante, QR pharma, BiOasis, and United Neuroscience. Dr. Cummings owns the copyright of the Neuropsychiatric Inventory. Dr. Cummings is supported by Keep Memory Alive (KMA); NIGMS grant P20GM109025; NINDS grant U01NS093334; NIA grant R01AG053798; and R35AG71476. JB has no disclosures. GL is a full-time employee of Biogen.

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How to cite this article: Cummings J, Bauzon J, Lee G. Who funds Alzheimer's disease drug development? *Alzheimer's Dement*. 2021;7:e12185. https://doi.org/10.1002/trc2.12185