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FEATURED ARTICLE

The costs of developing treatments for Alzheimer's disease: A retrospective exploration

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Abstract

Introduction: With the exception of the recent accelerated approval of aducanumab, in over 26 years of research and development (R&D) investment in Alzheimer's disease (AD), only five novel drugs—all for symptomatic treatment only—have reached FDA approval. Here, we estimate the costs of AD drug development during this period in the private sector.

Methods: To estimate private R&D funding, we collected information on AD clinical trials (n = 1099; phases 1–4) conducted between January 1, 1995 and June 21, 2021 from various databases. Costs were derived using previously published methodologies and adjusted for inflation.

Results: Since 1995, cumulative private expenditures on clinical stage AD R&D were estimated at $42.5 billion, with the greatest costs (57%; $24,065 million) incurred during phase 3; approximately 184,000 participants were registered or are currently enrolled in clinical trials.

Discussion: Measures to reduce expenditures while moving toward disease-modifying therapies that alleviate the rising burden of AD require continued investment from industry, government, and academia.

KEYWORDS
Alzheimer's disease, clinical trials, funding, industry, research and development

1 | BACKGROUND

1.1 | The high risk of drug development for Alzheimer's disease

Drug development and approval of effective and safe therapies that alter the clinical course of neurodegenerative diseases (NDD) have been especially challenging.[1] Although there have been some successes, and with the exception of the recent accelerated approval of aducanumab, the drugs approved for central nervous system (CNS) diseases are largely those that effectively treat disease symptoms rather than slowing disease progression or mitigating the underlying biological processes. This is the case in Alzheimer's disease (AD), which remains one of the most difficult therapeutic areas for drug development and has a near 100% failure rate.[2] Between 1995 and 2021, 878 drugs across all therapeutic areas have been approved by the US Food and Drug Administration (FDA); only six of these drugs are indicated for AD (four cholinesterase inhibitors [ChEIs], memantine, and aducanumab).

Because of the high risk and lack of commercial success associated with CNS drug development, many pharmaceutical companies have drastically curtailed their investments in CNS diseases over the past

20 years.[3–5] Such measures likely reflect concerns regarding the limited availability of target engagement biomarkers, complex clinical trial designs, imprecise clinical measures, heterogeneous symptoms, limited ability to affect the underlying causes of CNS diseases, and the lack of predictive animal models [6,7]—all of which contribute to high risk with uncertain future revenues. AD drug development is the canonical example of this predicament. AD drug trials cost more per patient than trials in any other therapeutic area, with 50% to 70% of the cost devoted just to patient screening.[8] Recruiting for AD trials is difficult, and participant attrition is high since the trials are often longer than trials in other therapeutic areas—especially for trials attempting to demonstrate disease modification and those focusing on secondary prevention.

1.2 | Development of symptomatic therapies for AD

It has been more than 28 years since the first drug to treat AD, tacrine, was approved in the US in 1993. The ChEIs tacrine, donepezil, rivastigmine, and galantamine were approved in 1993, 1996, 2000, and 2001, respectively, and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine was approved in 2003. Although a combination capsule containing memantine and donepezil was approved in 2014, no new novel AD therapies have been approved by the FDA since memantine in 2003, and tacrine is no longer marketed. Aducanumab's accelerated approval by the FDA marks the first AD treatment to address a defining pathology of the disease. Given the projected growth of the AD population and the tremendous personal, social, and economic costs of the disease, the demand for more new and effective treatments is more important than ever.

1.3 | Purpose of this analysis

The purpose of our investigation was to quantify the financial aspects of AD drug development in the private sector and the cost of bringing new treatments to patients. To that end, we examined the investment in private AD research over the past 26 years in terms of research and development (R&D) costs, patient participation, and drug development program discontinuations. We propose ways to reduce R&D costs while maintaining the rigorous search for more effective therapies.

2 | METHODS

2.1 | Data collection

To estimate private R&D funding in AD, we considered and consolidated information from multiple sources and databases: ClinicalTrials.gov, AdisInsight, PubMed, Alzforum, and GlobalData. First, agents that had reached clinical stage development in AD (as of June 11, 2021) were identified using alzforum.org. This initial list of 243 agents included multiple potential mechanisms of action in AD (eg, amyloid-related, tau, cholinergic system, neurotransmitters, inflammation, cholesterol, unknown, or other as categorized on alzforum.org). A known caveat of collecting such data from multiple secondary sources is that they may not be exhaustive, and thus there is a potential that some trials were excluded. Second, based on this initial list of 243 agents (and using individual agent names as search terms), records specific to 1132 trials were found using ClinicalTrials.gov and AdisInsight (Springer Nature); we deferred to ClinicalTrials.gov as the primary source (Figure 1). Third, of these trial records, eight agents (medical foods or medical devices; n = 35 trial records) were removed, and a total of 1097 trial records were manually confirmed for data analysis. Fourth, internet searches for press releases and other company information regarding agents, their clinical trials, program terminations, and asset discontinuations were used to complement the initial search methodology. For each clinical development program identified, we recorded the trial phase as of June 21, 2021, or the phase in which a trial had a negative outcome showing no drug-placebo difference; the number of trial participants; and the cumulative costs of the collective R&D for each candidate AD treatment based on the model described below.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors used multiple sources of information to determine the research and development costs in Alzheimer's disease (AD) from 1995 to present.
2. **Interpretation**: Our findings highlight the cumulative expense of conducting clinical trials in AD over the past quarter century ($42.5 billion), with the greatest costs incurred in late-stage drug development, and reveal the shift from research aimed at amyloid targets to that aimed at more diverse disease targets.
3. **Future directions**: AD is a pressing public health challenge, and new therapies are needed. The cost of AD drug development is high, and failures are common. Better means of reducing and distributing costs, sharing risks, and improving development success are needed.

RESEARCH IN CONTEXT

- Since 1995, private funding for clinical stage AD research has been US $42.5 billion
- The cost of AD drug development is high, and failures are common
- Better means to lower research cost burden and share risks are needed

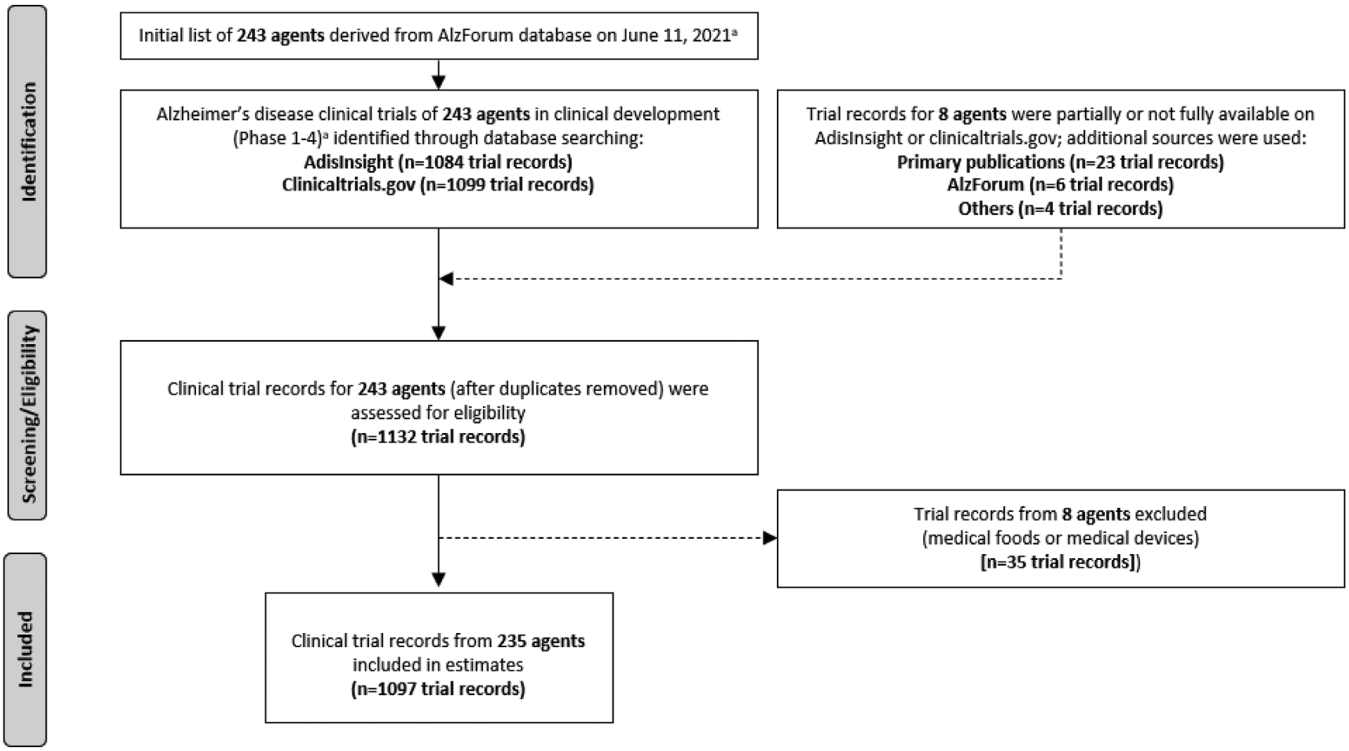

FIGURE 1 PRISMA flowchart of trial records included in the estimates. [a]Initial list of agents derived from those listed on Alzforum in June of 2021. These agents included those with potential mechanisms in key areas of study in AD: amyloid pathway, tau pathway, inflammation, and neurotransmitters. Agents with mechanisms that were not pursued by larger organizations or where dollar investment may be insignificant were excluded

2.2 | Data development

The number of trial participants was calculated from information listed on ClinicalTrials.gov for relevant trials. Where possible, we defaulted to intent-to-treat population estimates. In some cases, numbers of trial participants were found in published articles through PubMed or Alzforum.org therapeutic databases (using filters for "Alzheimer's disease" and phases 1, 1/2, 2, 2/3, 3, and 4). Search results were culled and inspected by two independent reviewers.

The overall cost of a drug development program was estimated based on the highest phase of clinical development (phase 1, 2, or 3) that was achieved for each investigational agent and based on data extracted from Scott et al. (2014).[7] Cumulative R&D expenditures associated with each stage were assigned per drug in development: $79 million for phase 1, $141 million for phase 2, and $462 million for phase 3 or phase 4; these estimates were adjusted for inflation to reflect 2021 US dollars using an inflation calculator[9] based on the latest data from the US Bureau of Labor and Statistics' Consumer Price Index.[10] For example, the total cost for a clinical development program in phase 3 was estimated as $462 million regardless of the number of phase 1-3 trials that have been conducted for that particular agent. Failure rate was calculated as discontinuations/(discontinuations + approvals). This analysis did not consider the cost of non-clinical studies or the costs incurred by patients and their families (eg, transportation, lost days of work, etc).

3 | RESULTS

3.1 | AD clinical trial failures and cumulative R&D costs

Since 1995, total private funding of AD R&D reached an estimated $42.5 billion. These expenditures have been devoted nearly exclusively to agents that have failed to reach approval (Figure 2, Table 1). Figure 1 shows the cumulative total of the private expenditures since 1995. Of 235 agents analyzed, 112 remain in active clinical development, six have reached commercialization, and 117 have had negative outcomes in various stages of clinical development (36 as late-stage failures; Table 1), equating to a 95% failure rate.

3.2 | Patient participation

Clinical trials can proceed only with participants who form a critical alliance with researchers and allow themselves to be assigned to a placebo or an active agent with unknown efficacy and safety. Time, effort, and commitment are required of both the participant and the care partner, who often serves as a surrogate reporter of trial information. In the 1097 AD drug trials conducted since 1995, 183,679 participants have entered or are currently enrolled.

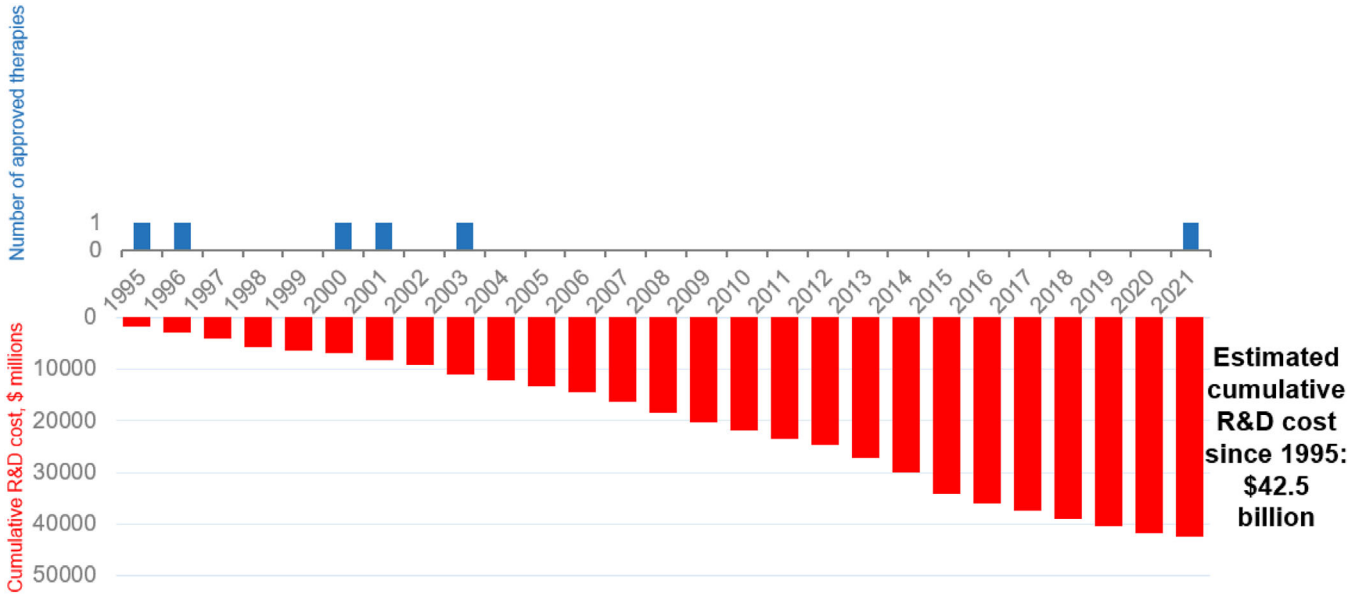

FIGURE 2 The collective cost of AD drug development since 1995. The graph illustrates the year-over-year cumulative estimated cost of drug development for agents in phases 1, 2, 3, and 4. R&D, research and development

3.3 | Distribution of AD R&D efforts

Clinical development of AD treatments has been aimed at a variety of disease targets, mostly synaptic dysfunction and the amyloid-β protein (Figure 3), with many advancing to phase 2 and 3 development. Figure 4 shows the highest clinical trial phases reached for drugs in development programs, both discontinued and ongoing, since 1995.

The highest costs ($24.1 billion) of R&D have been incurred during phase 3 development (Figure 5). The combined cost of phases 2 and 3 clinical development since 1995 (≈$33.7 billion) reflects the tremendous potential savings had mechanisms to identify lack of efficacy at early-stage development been available.

3.4 | ChEIs inform the innovation cycle

The development of ChEIs for AD sparked a cycle of innovation in AD treatments, leading to advances in our understanding of the disease process and the many potential therapeutic pathways, including those that might modify the disease course. Based on our assessment methodology, the estimated phase 3 development cost for donepezil, rivastigmine, and galantamine was $1.4 billion ($454 million each for having reached phase 3 development); however, this is likely an underestimation due to the large number of phase 3 clinical trials conducted for these drugs. Collectively, 29 phase 3 clinical trials have been conducted for these three drugs alone—representing 14.8% of all phase 3 AD trials conducted since 1995. The oral (capsule or tablet) formulations of the ChEIs each had market exclusivity for approximately a decade from the launch date. In the 12 months before loss of exclusivity for the tablet or capsule formulations, donepezil, rivastigmine, and galantamine had a combined global sales of ≈$5 billion.[2] By 2016, consumer expenditures on these agents had fallen to $1.4 billion due to the entry of generics.[2] Approximately half of all US patients diagnosed with AD receive treatment with ChEIs, indicating that millions of patients with AD have been treated with these agents since they were assigned generic status.[11]

4 | DISCUSSION

4.1 | The rising costs of AD

AD currently costs the US nearly $612 billion/year: $355 billion in direct costs (including $76 billion in out-of-pocket spending) and $257 billion in indirect costs.[12] For the individual patient with AD, lifetime costs can exceed $500,000 when diagnosed at age 75 years, with patients/families shouldering ≈86% of the net costs from informal caregiving and out-of-pocket payments.[13] The complete burden of this disease is exceedingly difficult to determine, but an effective therapy to prevent, delay, or alter its course has the potential to greatly reduce both measurable and immeasurable societal and personal costs.

4.2 | The cost of progress

According to a 2014 analysis, the total estimated cost to develop a treatment specifically for AD from the non-clinical stage to FDA approval was $5.7 billion and took >13 years to accomplish.[7] The

TABLE 1 Cumulative R&D statistics, 1995 to 2021

Year	Patients, n	Approved, n	Discontinued, n	Late-stage discontinuation, n	Failure rate, %	R&D, cost, $ millions
1995	13,870	1	1	1	50	1800
1996	19,642	2	2	2	50	3000
1997	30,790	2	3	2	60	4000
1998	34,558	2	4	2	67	5800
1999	36,519	2	6	3	75	6400
2000	39,591	3	11	7	79	6800
2001	43,709	4	13	8	76	8200
2002	44,919	4	15	8	79	9100
2003	51,116	5	15	8	75	11,000
2004	56,137	5	17	9	77	12,100
2005	64,801	5	21	12	81	13,400
2006	71,402	5	24	12	83	14,600
2007	81,832	5	30	15	86	16,200
2008	92,687	5	34	18	87	18,300
2009	104,904	5	42	22	89	20,300
2010	112,915	5	47	25	90	21,900
2011	117,651	5	50	25	91	23,400
2012	126,164	5	57	27	92	24,600
2013	137,698	5	65	28	93	27,300
2014	144,984	5	71	28	93	30,000
2015	159,520	5	81	28	94	34,100
2016	167,277	5	91	29	95	36,000
2017	169,472	5	95	29	95	37,400
2018	172,068	5	105	32	95	39,000
2019	173,775	5	113	34	96	40,400
2020	176,964	5	114	36	96	41,700
2021	183,679	6	117	36	95	42,500

Numbers represent cumulative totals of pharmaceutical research and development (R&D) out-of-pocket costs for agents in phase 1, 2, 3, or 4 development between 1995 and 2021.[9,11] For each calendar year, the status of each clinical development program (phase of development or whether the program resulted in an approved agent or discontinuation) was recorded in an Excel spreadsheet. A phase 3 program discontinuation was counted as a late-stage discontinuation. Failure rate was calculated as discontinuations/(discontinuations + approvals).
Additional R&D out-of-pocket costs were added to the cumulative total only when an agent reached the next phase in clinical development. Year-over-year R&D cost for each agent was also recorded in the Excel spreadsheet. The number of patients involved in each development program was synthesized based on information from ClinicalTrials.gov, AdisInsight database, primary publications, and Alzforum database. Summary statistics across 235 agents were calculated for each year, and year-over-year cumulative data is presented here.

methodology used in our study differs in that we focused only on the R&D costs for phases 1 through 4 of clinical development.

The current trajectory of costs for AD patient care is unsustainable and puts the costs of treatment R&D in perspective. Projected costs in the US alone are expected to surpass $1 trillion annually by 2050.[14] According to a 2015 Alzheimer's Association report, had an AD treatment breakthrough that delayed the onset of AD by 5 years been available in 2015, the cumulative reduction in total costs to all payers would have been $447 billion by 2050.[14] Savings in 2020 alone ($50 billion) could have financed the total investment in AD phase 1 to phase 4 drug development over the past 26 years. The impact of aducanumab on care costs is not yet known.

4.3 | NIH funding has an important impact

In addition to the private costs systematically captured in this review, a large portion of AD R&D is supported by public funding. It is more challenging to comprehensively capture these costs across the globe. Since 2008, the National Institutes of Health (NIH) has funded ≈$13 billion

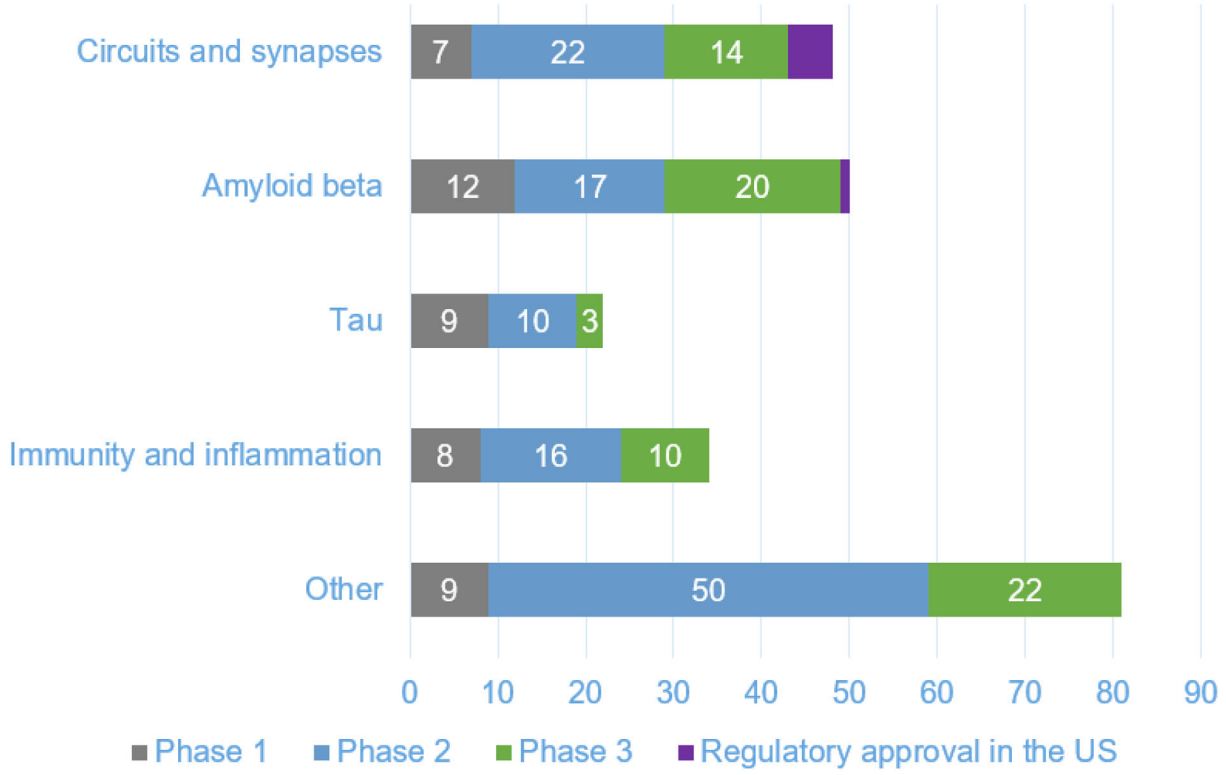

FIGURE 3 Agents in clinical development by key disease targets. The chart summarizes the highest development phase for each agent (n) in clinical development for Alzheimer's disease, categorized by the key disease targets as defined by the Common Alzheimer's Disease and Related Dementias Ontology[16]

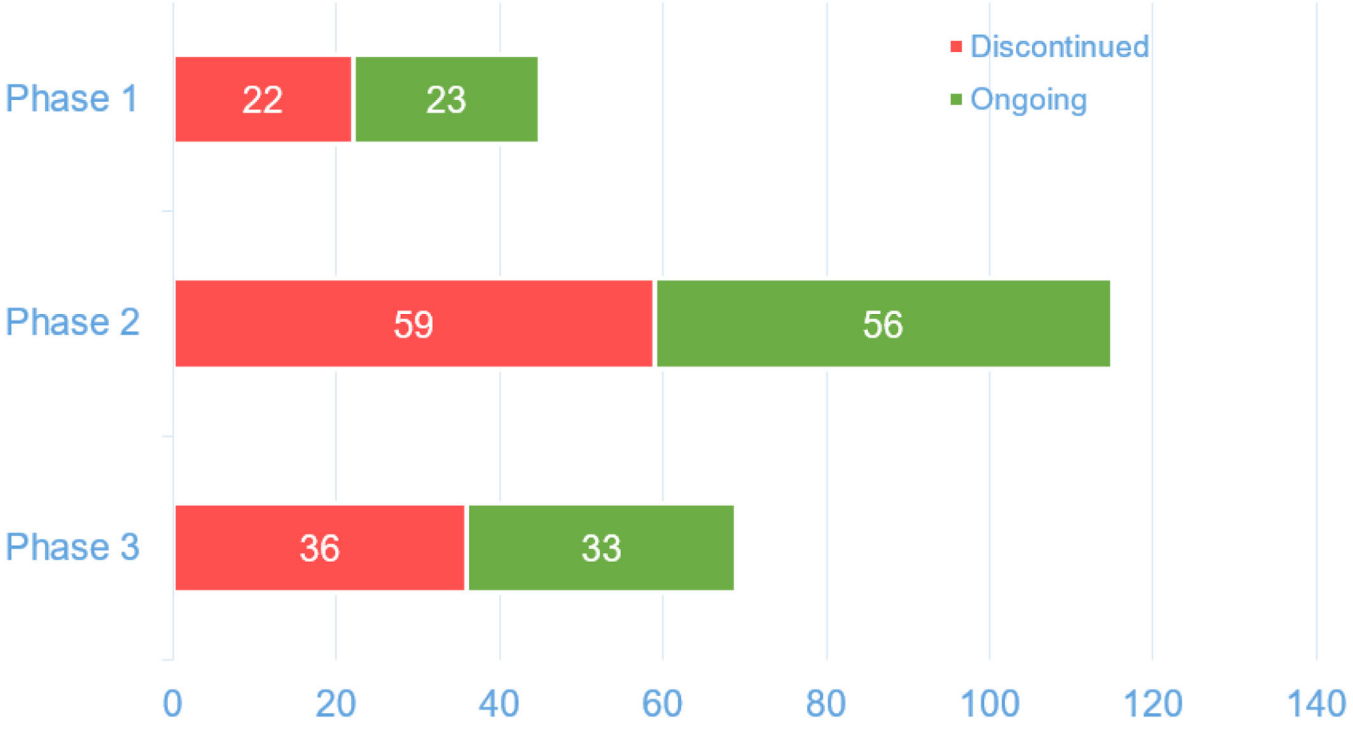

FIGURE 4 Highest clinical trial phase reached for agents in clinical development for Alzheimer's disease (AD). The chart summarizes agents (n) in clinical development for AD from 1995 to 2021, categorized by the highest clinical trial phase reached for discontinued (red) and ongoing (green) agents

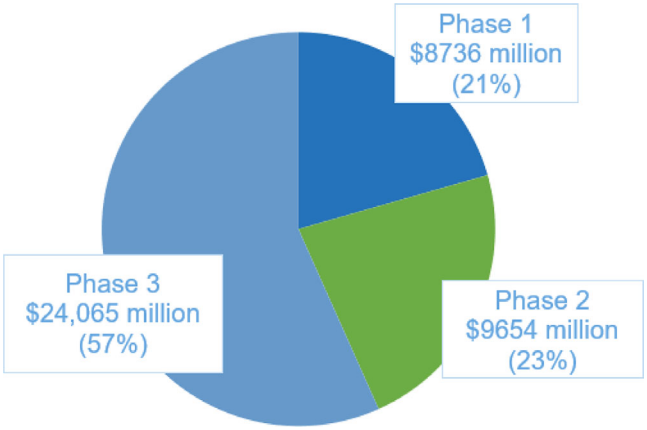

FIGURE 5 Drug development cost by clinical trial phase. The chart illustrates the estimated cost of AD drug development from 1995 to 2021 for agents in phases 1, 2, and 3

in AD research distributed through grants awarded by various administering institutes or centers. According to the International Alzheimer's and Related Dementias Research Portfolio (IADRP) database,[15,16] an additional $3 billion outside of NIH funding was invested in AD research between 2008 and 2020. Public funding devoted to basic research is critical to developing disease understanding, identifying targets for therapy, nominating therapeutic classes and agents, and discovering new biomarkers.

4.4 | Changing the AD trajectory

Although AD research has led to only six approved symptomatic treatments, the benefits of successful development of these drugs extend beyond providing new therapies to patients. Over the past 26 years, the field as a whole has gained understanding of the complex biology of AD, identified numerous potential targets for future drug development, developed new and informative biomarkers, extended the range of AD trial populations to include preclinical and prodromal states of AD, improved trial designs and measures, and enhanced the quality of trial conduct.

While R&D costs have increased in every therapeutic area, much of the expense of developing AD therapies lies in the difficulty of quickly and accurately identifying clinical trial participants. The field needs new targets with greater therapeutic potential, improved animal models, and reliable surrogate biomarkers that can signal efficacy or lack of effect earlier in clinical development. There is continued interest in the amyloid-β protein as a drug development target, and one drug addressing this target has been approved; analysis of the distribution of R&D investment suggests that there is progressive emphasis on non-amyloid targets.[17]

Approval of a disease-modifying therapy may begin to change the trajectory of the expected AD burden by 2050.[14] The high cost of drug development limits drug development and delays treatment advances. Our analyses identified two important areas where cost savings can be realized. First, the use of biomarkers—especially blood-based markers—may substantially reduce the cost of participant identification and enrollment.[18] Second, identifying failures earlier in the development process could reduce the high costs of unproductive phase 3 trials, decreasing overall R&D expenditures and therefore lowering direct medical costs for both patients and payers.

4.5 | Continuing investments in AD drug R&D

Although public funding has complemented private R&D and encouraged public-private research relationships, the financial responsibility for drug development has fallen largely on the pharmaceutical industry. In many therapeutic areas, including AD, the rising costs of drug development are neither sustainable nor desirable and may impede innovation. The financial risk of pursuing candidate AD drugs is exceptionally high, and comparatively few companies and academic laboratories have accepted the challenge of researching AD and other NDDs. More diversified sources of funding and collaboration between government, academia, and private and publicly traded companies, along with strategic policy measures aimed at supporting innovation,[19] could lead to numerous effective and affordable therapies. Although government funding for AD research has increased sixfold over the past 10 years, AD ranks 23rd in terms of NIH investment despite its position as one of the top 10 causes of death among Americans.[20] To bridge the gap between direct government budget allowances for AD research and the need for more research investment, expanded policies rewarding companies and investors who risk NDD R&D could incentivize research in notoriously difficult areas of innovation.

4.6 | ChEIs and the innovation cycle

Investment in the development of ChEIs for AD is greater than any other single-candidate AD agent, and their use is anticipated to continue into the foreseeable future as part of a treatment regimen with disease-modifying and other types of therapies.[21] The recognition of the cholinergic pathway as a target for development of ChEIs led researchers to examine additional pathways and potential therapeutic targets and several ChEIs with improved safety and tolerability profiles, and improved formulations were developed and approved soon after the vanguard agent. Following the exhaustion of market exclusivity and the availability of less-expensive generic alternatives, the cost of these symptomatic treatments has decreased substantially.[22] This illustrates the overall cycle of innovation in drug development whereby innovation is rewarded by market exclusivity for a period of time, prior to the entry of lower-priced generics, providing capital for the next wave of innovation and thereby extending benefits to patients beyond the period of exclusivity. In this manner, biopharmaceutical companies reinvest profits in R&D to discover and advance the next generation of novel medications.[23]

4.7 | Stimulating innovation

The success of the first disease-modifying therapy in AD has the potential to reinvigorate the AD R&D pipeline, empower cycles of additional innovation, and generate momentum toward future successes despite a long history of failures in AD drug development. The few successes in new drug approvals in the US for AD since 2003 suggest that additional means of attracting innovators are needed. The exit of many biopharmaceutical companies from CNS drug development indicates that current incentives are insufficient to keep companies engaged and accept the development risks. NDD drug development might be made more attractive with incentives pioneered in orphan drug development, including significant tax credits for qualified clinical testing, waiver of the marketing application fee required of sponsors at the time of submission to the FDA, and extended marketing exclusivity.[24,25] These incentives have attracted innovation and led to the development of efficacious drugs for rare diseases.[26] Similar incentives and other financial innovations could stimulate greater biopharmaceutical industry involvement in research for AD and other NDDs.

The frequent failures of late-stage clinical trials over the past decade also suggests a need for a new approach to AD drug development. A greater focus on earlier stages of the disease and innovative research models that simultaneously examine multiple disease pathways may close the gap in knowledge surrounding the relationship between the observed neuropathological degeneration and the cognitive/behavioral decline in patients.[27,28] Such strategies may uncover new pathways and mechanisms to modify the disease trajectory. Efforts to advance AD R&D efficiency may be well served by innovative funding models (eg, mega funds, biobonds) and expanded public-private partnerships, which have been used successfully in other therapeutic areas to stimulate R&D innovation.[28,29]

4.8 | Limitations

The current estimate of pharmaceutical R&D expenditures in phases 1 through 4 did not include non-clinical development costs or those incurred by patients and caregivers. It did not include significant investments in non-pharmacological approaches in managing AD. Additionally, because primary sources detailing expenditure and development history for each agent were not publicly available, estimates were based on limited information from multiple secondary sources, and data for all phases of development were not always available. Basing our estimates on the 2014 Scott et al. study[10] may have underestimated recent trial costs, as these estimates predated the use of expensive imaging biomarkers that have become more commonly used for diagnostic confirmation and outcomes in AD trials. One alternative approach to our review would have been to attempt to find individual public information (for example, SEC filings) provided by manufacturers for R&D. We chose not to pursue this approach because of the substantial limitations involved; no public record housing an exhaustive list of this information exists. Additionally, R&D costs per company are not reported in a manner discrete enough to attribute to a single agent or trial, thereby making a list specific to AD or exhaustive of the agents in development challenging.

4.9 | Where do we go from here?

The burden of AD to society is rising at an alarming rate, and innovative ways to slow this trend and develop new therapies are required. By incentivizing investment, redirecting these investments to new and innovative ways to advance drug development, and diversifying R&D funding across public, private, and academic entities, we may accelerate development of treatments that prevent, delay, or alter the disease course.

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CONFLICT OF INTEREST

J. L. Cummings has provided consultation to Acadia, Alkahest, Alzheon, AriBio, Avanir, Axsome, Behren Therapeutics, Biogen, Cassava, Cerecin, Cortexyme, EIP Pharma, Eisai, Foresight, GemVax, Genentech, Green Valley, Grifols, Janssen, Karuna, Merck, Novo Nordisk, Ono, Otsuka, ReMYND, Resverlogix, Roche, Signant Health, Sunovion, Suven, and United Neuroscience pharmaceutical and assessment companies. He has stock options in ADAMAS, AnnovisBio, MedAvante, and BiOasis. He owns the copyright of the Neuropsychiatric Inventory. He is supported by NIGMS grant P20GM109025, NINDS grant U01NS093334, NIA grant R01AG053798, NIA grant P20AG068053, and NIA grant R35AG71476. **D. P. Goldman** has received research support, speaker fees, travel assistance, or consulting income from the following sources: ACADIA Pharmaceuticals, Amgen, The Aspen Institute, Biogen, Blue Cross Blue Shield of Arizona, Bristol Myers Squibb, Cedars-Sinai Health System, Celgene, Edwards Lifesciences, Gates Ventures, Genentech, Gilead Sciences, GRAIL, Johnson & Johnson, Kaiser Family Foundation, National Institutes of Health, Novartis, Pfizer, Precision Health Economics, Roche, and Walgreens Boots Alliance. **N. Simmons-Stern** is an employee of Biogen. **E. Ponton** was an employee of Biogen at the time of this study.

REFERENCES

1. Gribkoff VK, Kaczmarek LK. The need for new approaches in CNS drug discovery: why drugs have failed, and what can be done to improve outcomes. *Neuropharmacology*. 2017;120:11-19.
2. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimer's Res Ther*. 2014;6:37.

3. Berger JR, Choi D, Kaminski HJ, et al. Importance and hurdles to drug discovery for neurological disease. *Ann Neurol*. 2013;74:441-446.
4. Choi DW, Armitage R, Brady LS, et al. Medicines for the mind: policy-based "pull" incentives for creating breakthrough CNS drugs. *Neuron*. 2014;84:554-563.
5. Rinaldi A. Setbacks and promises for drugs against Alzheimer's disease: as pharmaceutical companies are retreating from drug development for Alzheimer's, new approaches are being tested in academia and biotech companies. *EMBO Rep*. 2018;19:e46714.
6. Yokley BH, Hartman M, Slusher BS. Role of academic drug discovery in the quest for new CNS therapeutics. *ACS Chem Neurosci*. 2017;8:429-431.
7. Scott TJ, O'Connor AC, Link AN, Beaulieu TJ. Economic analysis of opportunities to accelerate Alzheimer's disease research and development. *Ann N Y Acad Sci*. 2014;1313:17-34.
8. Malzbender K, Lavin-Mena L & Hughes L et al. Key barriers to clinical trials for Alzheimer's Disease. Leonard D Schaaeffer Center for Health Policy & Economics. 2020.
9. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2019. *Alzheimers Dement (N Y)*. 2019;5:272-293.
10. US Bureau of Labor Statistics. *Consumer Price Index*. https://www.bls.gov/cpi. Accessed June 25, 2021.
11. Bent-Ennakhil N, Coste F, Xie L, et al. A real-world analysis of treatment patterns for cholinesterase inhibitors and memantine among newly-diagnosed Alzheimer's disease patients. *Neurol Ther*. 2017;6:131-144.
12. Alzheimer's disease facts and figures. *Alzheimer's Dement*. 2021;17:327-406.
13. Jutkowitz E, Kane RL, Gaugler JE, et al. Societal and family lifetime cost of dementia: implications for policy. *J Am Geriatr Soc*. 2017;65:2169-2175.
14. *Alzheimer's Association. Changing the Trajectory of Alzheimer's Disease: How a Treatment by 2025 Saves Lives and Dollars*. https://www.alz.org/media/documents/changing-the-trajectory-r.pdf. Accessed June 25, 2021.
15. Liggins C, Snyder HM, Silverberg N, et al. International Alzheimer's Disease Research Portfolio (IADRP) aims to capture global Alzheimer's disease research funding. *Alzheimer's Dement*. 2014;10:405-408.
16. International Alzheimer's and Related Dementia Research Portfolio. Common Alzheimer's and Related Dementias Research Ontology (CADRO). 2021.
17. Cummings JL, Lee G, Ritter A, et al. Alzheimer's disease drug development pipeline: 2020. *Alzheimer's Dement (N Y)*. 2020;6(1):16.
18. Mattke S, Cho SK, Bittner T, et al. Blood-based biomarkers for Alzheimer's pathology and the diagnostic process for a disease-modifying treatment: projecting the impact on the cost and wait times. *Alzheimer's Dement (Amst)*. 2020;12:e12081.
19. Goldman DP, Fillit H, Neumann P. Accelerating Alzheimer's disease drug innovations from the research pipeline to patients. *Alzheimer's Dement*. 2018;14:833-836.
20. National Institutes of Health Estimates of funding for various research, condition, and disease categories (RCDC). https://report.nih.gov/funding/categorical-spending#/. Accessed June 25, 2021
21. Cummings JL, Tong G, Ballard C. Treatment combinations for Alzheimer's disease: current and future pharmacotherapy options. *J Alzheimer's Dis*. 2019;67:779-794.
22. Schneider LS, Mangialasche F, Andreasen N, et al. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. *J Intern Med*. 2014;275:251-283.
23. Moreno SG, Epstein D. The price of innovation - the role of drug pricing in financing pharmaceutical innovation. A conceptual framework. *J Mark Access Health Policy*. 2019;7:1583536.
24. Le TT. Incentivizing orphan product development: United States food and drug administration orphan incentive programs. *Adv Exp Med Biol*. 2017;1031:183-196.
25. Mueller CM, Rao GR, Miller Needleman KI. Precision medicines' impact on orphan drug designation. *Clin Transl Sci*. 2019;12:633-640.
26. Burke KA, Freeman SN, Imoisili MA, Cote TR. The impact of the Orphan Drug Act on the development and advancement of neurological products for rare diseases: a descriptive review. *Clin Pharmacol Ther*. 2010;88:449-453.
27. Khachaturian ZS, Khachaturian AS. The paradox of research on dementia-Alzheimer's disease. *J Prev Alzheimers Dis*. 2016;3:189-191.
28. Lo AW, Ho C, Cummings J, Kosik KS. Parallel discovery of Alzheimer's therapeutics. *Sci Transl Med*. 2014;6(241):241cm5
29. Goldman M, Compton C, Mittleman BB. Public-private partnerships as driving forces in the quest for innovative medicines. *Clin Transl Med*. 2013;2:2.

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