

The State of Innovation in
Highly Prevalent Chronic Diseases

Volume IV: Alzheimer's Disease Therapeutics

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BIO INDUSTRY ANALYSIS



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Introduction

This is the fourth report in a series on the innovation landscape of highly prevalent, chronic diseases. In our previously published research, emerging company investment for drug development in many of these common diseases was shown to be declining and low relative to total healthcare costs (**Figure 1**). This prompted the ongoing investigation to determine if the slowdown is industry-wide, beyond privately funded companies.¹ Thus far, we have identified a broader contraction of R&D in depression, pain, addiction, type II diabetes, and obesity.² The persistence of this trend could have implications for the future output of innovative medicines in these disease areas. The cause for concern is magnified by the impact these chronic disease areas have on the overall healthcare system in the US. Thus, it is important that barriers to therapeutic innovation are identified and removed.

This volume takes an in depth look at the state of innovation for therapeutics in Alzheimer's disease, a devastating highly prevalent chronic disease. Alzheimer's disease comprises up to 80% of all diagnosed dementia, which affects 5.7 million people in the U.S. alone and costs the U.S. healthcare system \$277 billion annually, with Medicare and Medicaid shouldering \$186 billion (67%) of the total.³ The growing Alzheimer's disease epidemic is expected to affect more than 13.8 million people in the U.S. by 2050, and cost well over \$1 trillion annually.⁴ Global estimates for dementia by 2050 suggest close to 152 million people with a cost at over \$2 trillion annually.⁵

Herein, we analyze disease-modifying drug candidates progressing through the clinical pipeline. The analysis aims to assess the depth and breadth of innovation to meet the urgent needs of patients suffering from Alzheimer's disease. Historical clinical success rates and failed mechanistic strategies are identified, as well as trends in venture financing and investment into new clinical trials.

Key Takeaways for Alzheimer's Disease

- **Marketed drugs:** There are currently no FDA approved disease-modifying drugs for Alzheimer's disease.
- **Venture investment:** Venture capital funding of U.S. companies with lead stage programs in Alzheimer's disease is 16 times below oncology funding (\$1.0 billion vs. \$16.5 billion over the last decade).
- **R&D success rate:** Clinical development success for disease-modifying drug programs for Alzheimer's has been difficult in late-stage trials, with no disease-modifying drugs moving beyond Phase III to FDA filing. Since the start of 2008, a total of 87 clinical-stage disease-modifying programs have been suspended. Disease-modifying drug programs moving from Phase I to Phase II have experienced a 47% probability of success (vs. 59% across all disease areas). Phase II to Phase III success is lower, with only a 36% probability of success (vs. 31% across all disease areas).
- **Clinical trial initiations:** Clinical trial starts for disease-modifying Alzheimer's drugs have ranged from 11-21 trial starts per year since 2008 with no detectable trend. Phase III trial starts have been the least consistent, ranging from 0-5 per year.
- **Pipeline:** There are 74 clinical-stage programs with disease-modifying potential in Alzheimer's disease. The drug candidates in these programs are attempting to stop, prevent, or slow the progression of Alzheimer's disease using 10 strategies involving 30 distinct molecular targets. Small emerging companies account for 77% of the Alzheimer's clinical programs.

¹ Thomas, D., Wessel, C. BIO Industry Analysis. Emerging Company Trend Report, (2018) (www.bio.org/iareports)

² Thomas, D., Wessel, C. BIO Industry Analysis. Highly Prevalent Chronic Disease Series, (2018) (www.bio.org/iareports)

³ Alzheimer's Association. 2018 Alzheimer's Disease Facts and Figures. <https://www.alz.org/alzheimers-dementia/facts-figures>

⁴ Alzheimer's Association. 2018 Alzheimer's Disease Facts and Figures. (page 23). The cost of caregiver support adds an extra \$237 billion in costs.

⁵ Alzheimer's disease International. World Alzheimer Report 2018. <https://www.alz.co.uk/research/world-report> (accessed March 2019)

U.S. HEALTHCARE COST VS. U.S. VENTURE CAPITAL FUNDING OF NOVEL R&D FOR HIGHLY PREVALENT CHRONIC DISEASES

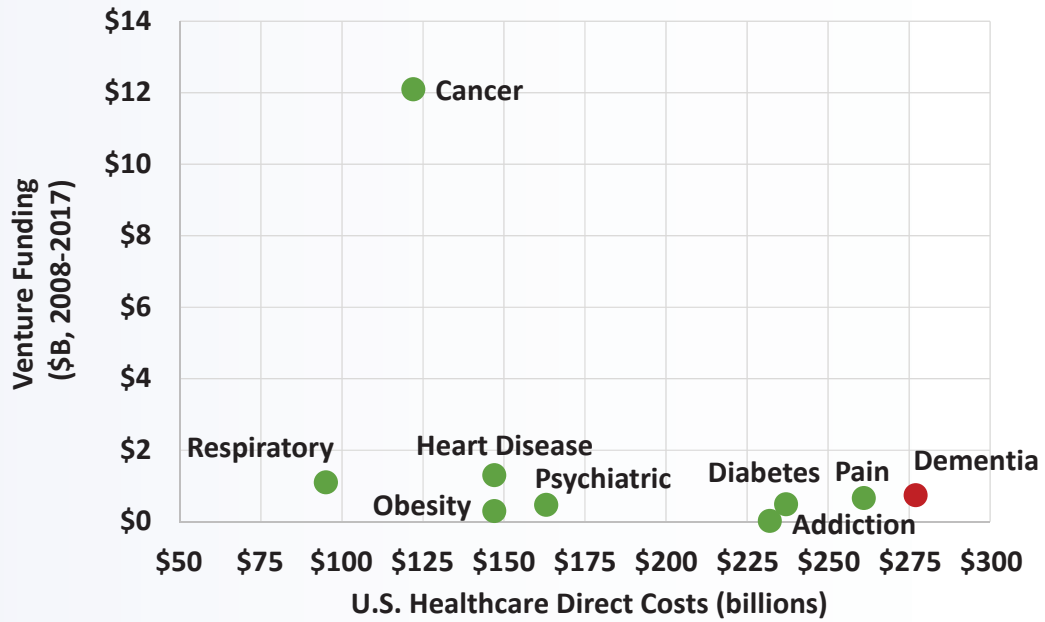


Figure 1. Healthcare Cost vs. Venture Capital Funding into novel chemical entity development 2008-2018 for Oncology and highly prevalent chronic diseases. Source for healthcare costs – Dementia: Alzheimer’s Association, 2018. Diabetes: March 2018 ADA report; Obesity, Heart Disease, Respiratory, Oncology are based on 2013 data cited in Health Affairs, 35, No. 6 (2016); Pain: The Journal of Pain, 2012; Addiction: NIDA website 2018. Source for venture data: BIO Industry Analysis, Emerging Company Trend Report, 2008-2017 (accessed in June 2018 at www.bio.org/iareports).

Alzheimer's Disease - Background

Alzheimer's disease is a complex chronic disease characterized biologically by the accumulation of extracellular protein plaques, neurofibrillary protein tangles, a loss of functional synaptic connections, and eventually complete loss of neurons. The loss of neuronal activity often begins in regions of the medial temporal lobe, an area deep inside the brain where long-term memory is consolidated.⁶ Clinically, it is a type of dementia characterized by progressive deterioration in cognition and memory, and impairment in the ability to carry out activities of daily living.⁷

Most cases of Alzheimer's are diagnosed later in life (over the age of 65); however, Alzheimer's can appear as early as 40 years of age. Because of this observation, the disease can be referred to as early-onset and late-onset Alzheimer's. A detailed categorization of the disease progression includes a pre-symptomatic phase, called "preclinical-stage Alzheimer's", a "prodromal-stage" characterized by mild cognitive impairment (MCI), followed by mild, moderate, and severe stages of dementia.⁸

Early-onset Alzheimer's disease occurs in 5% of patients with many patients having genetic mutations in genes associated with neuronal protein and lipid processing.⁹ A number of these genes are specifically associated with the trafficking and processing of amyloid protein, a drug target that will be discussed in more detail below.

Scientists have also identified genes involved in late-onset Alzheimer's disease, a far more common form of the disease through genome wide association studies. More than two dozen genes are known to correlate with increased risk of late-onset Alzheimer's. A recent study funded by the NIH, and the largest conducted to date, found five new genes, in addition to many previously identified genes, from a genomic screen of 35,000 individuals with late-onset Alzheimer's.¹⁰ The new genes and the previously identified genes have functional roles in pathways currently targeted for drug development, such as amyloid and /or tau clearance described in more detail below.

A well-known gene mutation associated with late-onset Alzheimer's is the ApoE gene variant, ApoE4. This gene codes for apolipoprotein E, a critical protein for dendritic lipid and protein trafficking required for synaptic plasticity and other changes involved in long-term memory, neuron growth and maintenance. In the case of ApoE4 gene carriers, lipid and protein trafficking is impaired and cognitive decline is much more rapid.¹¹ Interestingly, another less common gene mutation, known as ApoE2, is associated with a lower probability of developing late-onset Alzheimer's.¹² Clues such as this have provided direction for drug developers seeking to uncover the root cause or key molecular influencers of the disease.

⁶ Within the temporal lobe is the entorhinal cortex, the hub connecting the neocortex to the hippocampus. Pathological markers of Alzheimer's disease have been shown to spread from the entorhinal neocortical area to the hippocampus, and then to other areas of the brain. Querfurth, H., et al. Mechanism of Disease, Alzheimer's Disease. NEJM 362, 4, p.329-344 (2010)

⁷ Jalbert, J., et al. Dementia of the Alzheimer Type. Epidemiologic Reviews, 30 (1) p15-34 (2008)

⁸ <https://www.brightfocus.org/alzheimers/question/what-are-stages-alzheimers-disease>

⁹ Three genes identified with early-onset are APP (Amyloid Precursor Protein, PSEN1 and PSEN2 (genes for enzymes of the gamma secretase complex that cuts APP to form amyloid). See more at: <https://www.nia.nih.gov/health/alzheimers-disease-genetics-fact-sheet>, and <https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers/art-20048356>

¹⁰ Kunkle, B., et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates A β , tau, immunity and lipid processing. Nature Genetics, 51 p414-430 (2019)

¹¹ Aisen, P., Cummings, J., et al. On the path to 2025: understanding the Alzheimer's disease continuum. Alzheimer's Research & Therapy, 9 (60) (2017)

¹² Yu, J., et al. Apolipoprotein E in Alzheimer's Disease: An Update. Annual Review Neuroscience, 37 p79-100 (2014). Note that the most common ApoE form is ApoE3 and that the other two alleles (ApoE4 and ApoE2) produce apolipoprotein with single amino acid differences in the lipid binding domain.

Despite the identification of gene mutations associated with Alzheimer's Disease, many unknowns remain. For example, individuals without specific gene mutations know to be associated with Alzheimer's develop the disease. Others progress through life without clinical dementia yet have the hallmark brain signatures (such as plaques and fibrillary tangles).¹³ Furthermore, epidemiological studies correlate increased risk of developing Alzheimer's Disease in individuals with diabetes, obesity, hypertension, and individuals who smoke.¹⁴

Recent studies have also shown that lack of sleep may be a potential contributing factor. A January 2019 study detected higher tau and amyloid β (targets within the clinical pipeline discussed below) in individuals with poor slow wave sleep.¹⁵ Last year, an NIH funded study demonstrated an increase in amyloid levels after losing just a single night of sleep.¹⁶ During sleep, the brain undergoes much of the clearing of unwanted protein debris that builds up during waking hours. In the aging brain, this clearance system, known as the glymphatic system, slows and sleep disruption has long been correlated with early stages of cognitive decline.¹⁷

Furthermore, chronic stress, head injuries, gum disease, patient lifestyles (such as physical activity and diet), and various environmental exposures (such as metals and infectious agents), may all play a role in the progression of Alzheimer's disease. Large population studies, perhaps with the help of real-world data collection technologies, will give us additional clues to unravel this complex and varied disease.

In this report we review molecular targets that have been validated preclinically and are now in clinical development for Alzheimer's disease. Each program is grouped by the overall hypothesis-driven strategy taken to target this deadly disease. Although many molecular targets discussed below have been found to correlate with disease symptomology, no molecularly targeted disease-modifying drug has been approved by a regulatory agency. Only four symptom-modifying drug entities have been FDA approved, as described in the **Appendix**. These marketed drugs do not block the progression of the disease. This is unfortunate for the millions of families struggling with this disease but underscores how complex this disease is and how difficult it has been to intervene clinically.

¹³ Corrada, M., et al. A population-based clinicopathological study in the oldest. *Current Alz. Research* 9 p709-717 (2012). This study showed 50% of non-dementia brains autopsied had Alzheimer's pathology (see Figure 2 in the study).

¹⁴ Aisen, P., Cummings, J., et al. On the path to 2025: understanding the Alzheimer's disease continuum. *Alzheimer's Research & Therapy*, 9 (60) (2017)

¹⁵ Lucey, B., et al. E Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Science Translational Medicine*, 11 (474) (2019)

¹⁶ Shokri-Kojori E, et al. β -Amyloid accumulation in the human brain after one night of sleep deprivation. *PNAS* 115 (17) p4483-4488 (2018). Also, see <https://www.nih.gov/news-events/lack-sleep-may-be-linked-risk-factor-alzheimers-disease>

¹⁷ Boespflug, E., et al. The Emerging Relationship Between Interstitial Fluid-Cerebrospinal Fluid Exchange, Amyloid- β , and Sleep. *Biological Psychiatry*, 83 p328-336 (2018)

Clinical Pipeline - Therapeutic Approaches

The total clinical pipeline for Alzheimer’s disease contains 120 drug programs with 74 potentially disease-modifying and the remaining 46 intended to modify cognitive symptoms of the disease. For the purpose of this report, our analysis of the pipeline will focus only on the 74 disease-modifying clinical programs that are aimed at stopping or reversing the progression of the disease. A breakdown of symptom-modifying drug programs can be found in **Appendix A1**, which includes anti-psychotic, anti-depression, and other mood enhancing or cognition stimulating drugs, that act primarily on neurotransmitter pathways (i.e. acetylcholine and glutamate).

In **Figure 2a**, the 74 disease-modifying clinical programs are shown by phase of development. In **Figure 2b**, they are organized by mechanism of action. More than 80% of the 74 novel programs are split between Phase I (27) and Phase II (34). Only 13 programs (20%) are in phase III.

CLINICAL-STAGE DRUG PIPELINE OF DISEASE-MODIFYING THERAPETUICS FOR ALZHEIMER’S DISEASE

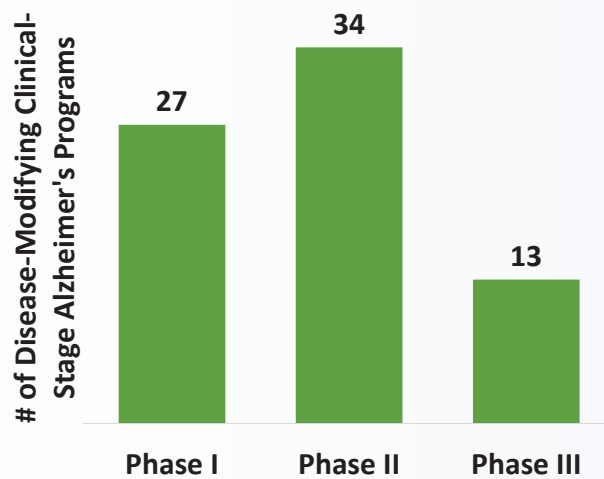


Figure 2a. The currently active Alzheimer’s disease clinical pipeline by phase (as of February 28, 2019, n=74), based on Biomedtracker’s classification methodology by phase of development as well as company website information. Twelve programs listed as “Ex-US” in the Biomedtracker database are included here by phase based on independent research of company websites. This “Ex-US” listing implies the companies have not yet intended to seek FDA approval. No NDA/BLA filings were active for Alzheimer’s Disease as of February 28, 2019. Only novel approaches with disease modifying potential in Alzheimer’s disease are shown.

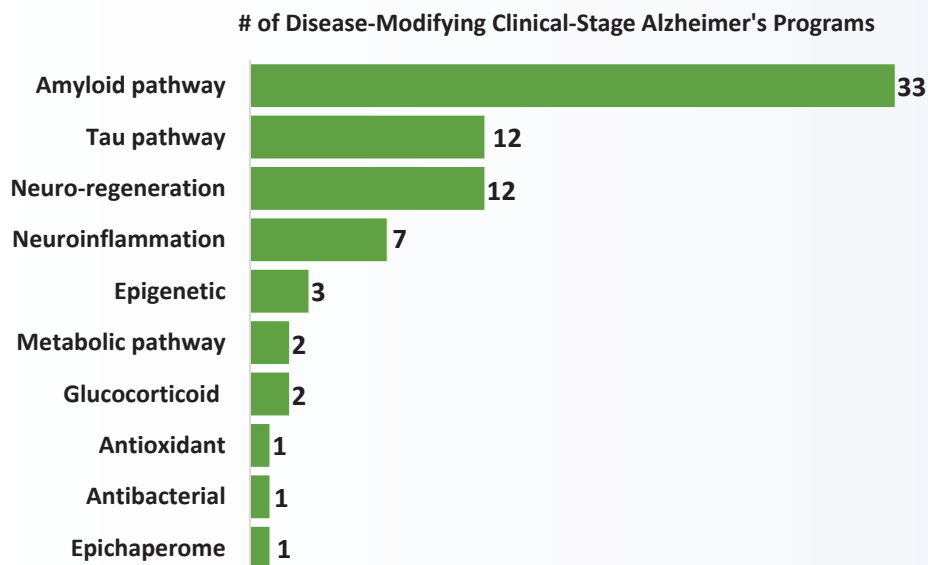


Figure 2b. The number of programs in each of the 10 target strategies in the Alzheimer’s disease clinical pipeline.

Over the last decade, there has been significant progress in advancing our understanding of the biological mechanisms underlying Alzheimer's disease. This is exemplified in the range of pipeline strategies, with 10 broad approaches that may potentially halt or reverse the progression of the disease (**Figure 2b**). Some of these approaches are likely interconnected, with some dependent on others, or existing in complex feedback loops that could eventually make all of them implicated in the disease. The interplay of different pathways involved in the pathology of Alzheimer's illustrates the complexity of this disease.

The most pursued approaches target the buildup of nefarious forms of amyloid β or tau protein (n=45, 60% of the pipeline). These two proteins, and their various forms, are the hallmark signals of the brain's potential progression toward cognitive decline. It is possible that the other eight approaches play a role either downstream or upstream of amyloid β and tau accumulation but have been separately categorized herein due to the wide range of other pathways they are involved in. The other eight approaches (as show in **Figure 2a and 2b**) are categorized into the following categories: neuro-regeneration (n=12), inflammation pathways (n=7), epigenetic (n=3), metabolic/energy pathways (n=2), glucocorticoids/cortisol (n=2), antioxidant (n=1), antibacterial (n=1), and the epichaperome (n=1).

Driving these diverse approaches are the small emerging companies, accounting for 77% of all clinical programs. Roughly 40% of these small company programs are partnered .

For the Phase III programs, 10 are amyloid focused and the other three target tau, inflammation, or metabolic pathways. The only categories that do not currently have a Phase II or Phase III are the antioxidant (n=1), antibacterial (n=1), and the epichaperome approaches which are all in Phase I testing. However, as will be described below, the antioxidant pathway has seen three failures in the last decade at more advanced stages. Compared to the other strategies, the antibacterial and epichaperome approaches are more recent approaches without history of prior clinical program work. As will be discussed later, the remaining eight strategies have a history of failed programs over the last decade.

2019 ALZHEIMER'S DISEASE CLINICAL PIPELINE BY SUB-STRATEGY AND PHASE

Strategy	Sub-Strategy	Phase I	Phase II	Phase III	Clinical Programs
Amyloid Pathway	removal/clearance (Mab)	3	2	3	8
	removal/clearance (non-Mab)	3	6	2	11
	slowing production	1	4	2	7
	disaggregation	2	2	3	7
Tau Pathway	removal/clearance (Mab)	1	4	0	5
	removal/clearance (non-Mab)	1	1	0	2
	slowing production	1	2	0	3
	disaggregation	0	0	1	1
	stabilization (microtubules)	1	0	0	1
Neuro Regeneration	growth/neurotrophic proteins	4	1	0	5
	cell therapy	1	3	0	4
	sigma receptors	0	1	0	1
	plasma fraction	0	1	0	1
	unknown	0	1	0	1
Neuro Inflammation	signaling (kinases)	1	1	1	3
	leukotrienes (CysLTR)	0	1	0	1
	macrophages (chlorite/taurine)	1	0	0	1
	microglia (TREM2)	1	0	0	1
	potassium channels	1	0	0	1
Epigenetic	bromodomains	1	0	0	1
	histone deacetylase	0	1	0	1
	histone demethylase	0	1	0	1
Metabolic	ketogenic (lipids)	0	0	1	1
	glycolytic/ketogenic (PPAR)	0	1	0	1
Glucocorticoid	cortisol (11 β -HSD)	1	1	0	2
Antioxidant	reactive oxygen species (mPES-1)	1	0	0	1
Antibacterial	protease	1	0	0	1
Epichaperome	epichaperome	1	0	0	1
	Total	27	34	13	74

Figure 2c. The breadth of target sub-strategies in the current disease-modifying Alzheimer's clinical pipeline listed by phase of development. Data for program phase was obtained from Biomedracker. Mab, Monoclonal antibody.

Strategy #1 – Targeting the Amyloid Pathway

The most heavily researched and drug-targeted pathway relates to amyloid β formation in the brain. In the brains of Alzheimer's patients, amyloid extracellular plaques are found in three forms (amorphous, nonfibrillar, and fibrillar). This small amyloid protein is generated on neuronal membranes when its precursor form is cleaved by protease enzyme complexes. This cleavage can generate different length amyloid protein, such as the 1-40 and 1-42 amino acid lengths, as the most prominent forms and can accumulate extracellularly. However, it is the oligomeric form of amyloid $\beta_{(1-42)}$ in particular that is correlated with pathophysiological events, such as synaptic dysfunction, Tau hyperphosphorylation (discussed below), mitochondrial dysfunction, and neuronal stress or death.

In the current pipeline, there are 33 drug programs targeting the amyloid pathway. These can be grouped into three sub-strategies: 1) drugs targeting the removal or clearance of amyloid β from the brain (for example, via antibody), 2) drugs that break up amyloid aggregated or disrupt its binding to other receptors or cofactors involved in the pathology of Alzheimer's disease, or 3) drugs that prevent or slow the production of amyloid β (for example, shifting the processing of amyloid precursor protein, APP).

- 1. Removal/clearance of amyloid.** This has been the area with the highest concentration of R&D within Alzheimer's drug development.¹⁸ Removal of amyloid $\beta_{(1-42)}$, and its varied oligomeric and aggregated forms, has been hypothesized to decrease its toxic effects and possibly stop the progression of neuronal damage. This continues to be pursued through the use of antibodies (n=8 programs) that directly bind to amyloid, as well as vaccines aimed at training the native immune system to produce anti-amyloid antibodies (n=6 programs). The natural removal of amyloid is carried out through a clearance processes known as the glymphatic clearing system and is active at night. This system may not work sufficiently in the aged brain. It is possible that key proteins, such as purine receptors, ATP-binding cassette transporters, and even albumin can make this process more efficient. There are five drug programs in the pipeline taking this approach. Interestingly, ApoE, a key protein believed to act as a chaperone for amyloid (and other proteins and lipids), is not a direct target found in the current clinical pipeline.
- 2. Disaggregate/disrupt amyloid.** These drugs prevent amyloid proteins from binding together, blocking aggregation, or they can act to disrupt unfavorable interaction of amyloid and certain receptors. One example from the pipeline is a small molecule that blocks the filamin A scaffolding protein and its binding of toxic amyloid species to acetylcholine receptors. This filamin A blockage reduces the secondary effect of signaling to tau phosphorylation and pro-inflammatory cytokine release (via toll-like receptor 4).¹⁹ There are currently seven molecules in the clinic that act through a disaggregating/disrupting process.
- 3. Prevent/slow the production of amyloid.** As amyloid β is a byproduct of cleaved APP, either slowing or shifting the cleavage of APP to the less toxic amyloid $\beta_{(1-40)}$ form is a strategy employed by seven drugs. The beta secretase (BACE) and gamma secretase inhibitors exemplify this strategy. Although there have been numerous failures (discussed below) three secretase inhibitors remain active in clinical trials. Another four approaches have less direct evidence of modulating APP processing, but biochemical evidence suggests they can slow or block APP production itself.^{20,21} As an example, the enzyme PKC is involved in physiological processes related to learning and memory, but its activation has also been shown to slow amyloid as well as tau aggregation (by either shifting secretase toward sAPP or slowing the phosphorylation of tau).²²

¹⁸ Panza, F., et al. A critical appraisal of amyloid- β -targeting therapies for Alzheimer disease. *Nature Reviews Neurology*, 15 p73-88 (2019)

¹⁹ Wang, H., et al. Reducing amyloid related Alzheimer's disease pathogenesis by a small molecule targeting filamin A. *J. Neurosci.* 32, p9773-9784 (2012)

²⁰ Teich, A., et al. Posiphen Translational inhibition of APP by Posiphen: Efficacy, pharmacodynamics, and pharmacokinetics in the APP/PS1 mouse. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* 4 p37-45 (2018)

²¹ Melnyk, P., et al. Chloroquine and Chloroquinoline Derivatives as Models for the Design of Modulators of Amyloid Peptide Precursor Metabolism. *CS Chem. Neurosci.* 6(4), p559-569 (2015)

²² Talman, V., et al. Protein Kinase C Activation as a Potential Therapeutic Strategy in Alzheimer's Disease: Is there a Role for Embryonic Lethal Abnormal Vision-like Proteins? *Basic Clinical Pharmacology Toxicology* 119(2) p.149-160 (2016) (see Fig. 3)

Strategy #2 – Targeting the Tau Pathway

The second most pursued strategy, and one that has had increasing interest in recent years, in part due to the lack of success with amyloid targeting drugs, is the targeting of malfunctioning tau protein, either directly or indirectly. As far back as the 1980s researchers have known that tau plays a role in the pathology of the disease.²³ The tau protein is an essential stabilizing component for neuronal microtubules and may serve a role in cell signaling.²⁴ Microtubules are key building blocks in cells, but also facilitate transport of vesicles containing neurotransmitters. When tau becomes unstable, the microtubules can fall apart, disrupting neuron function.

Tau protein can be destabilized by phosphorylation, but it is possible that other post-translational modifications (acetylation, glycosylation, etc.) contribute to its demise.²⁵ Once the state of tau is altered, tau can form fibrils inside the cell and can also be excreted and passed on to other cells.²⁶

In the pipeline, there are 12 drug programs under the tau targeting approach as shown in **Figure 2c**. These can be grouped into three sub-strategies: 1) drugs that target the removal or clearance of tau from the brain (for example, via antibody), 2) drugs that prevent tau aggregation or disrupt abnormal tau activity, 3) drugs that prevent or slow the production of tau (for example, using antisense to block translation), or 4) drugs that stabilize microtubules.

- 1. Removal/clearance of tau.** This is the sub-strategy with the most R&D activity for tau targeting, with seven of the 12 drug programs aimed at the direct removal or clearance of tau. Five of the seven drugs target tau via monoclonal antibodies, with four of these in Phase II and one in Phase I. These antibodies act extracellularly and are thus designed to intercept the cell-to-cell spread of pathological Tau. They likely differ in epitope binding and in their affinity for aggregated states of tau.²⁷ Another tau clearing approach is to create a vaccine against the pathological form of the tau protein. There is one Phase II and one Phase I program underway that aim to stimulate an immune response against tau and thus prevent the formation of tau oligomers and neurofibrillary tangles. A final drug program aims to use purine receptor activation to allow for tau mobilization, a potential gateway open during the glymphatic system mentioned above.
- 2. Disaggregate/disrupt tau.** The drug program furthest along in the pipeline has been in various clinical trials over the last 10 years and in Phase III trials since 2012 but has seen multiple setbacks with different formulations. This drug works to prevent the aggregation of tau.²⁸
- 3. Prevent/slow the production of tau.** Two drugs under the tau strategy target the post-translational modifications of tau, such as phosphorylating/dephosphorylating, thought to promote tau instability. There are two of these drugs in the clinic, one is a Phase II program drug that works by inhibiting a kinase and the other a Phase I program testing a phosphatase agonist. A third drug works via anti-sense to down-regulate tau gene expression. Lowering levels of tau by intervening at the translational level has, in mouse studies, been shown to prevent neuronal loss and tauopathy.²⁹
- 4. Microtubule stabilization.** There is one microtubule stabilizing agent, derived from the structure of Taxol, in Phase I. Taxol is used to prevent otherwise rapidly dividing cancer cells from dividing as it binds microtubules, preventing the depolymerization needed for cell division. Such chemical stabilization of microtubules could be mimicking the role tau plays in neuron microtubule stabilization.

²³ Manelkew, E., et al. Biochemistry and Cell Biology of Tau Protein in Neurofibrillary Degeneration. Cold Spring Harb Perspect Med. 2(7) a006247 (2012)

²⁴ Jadhav, S., et al. A walk through tau therapeutic strategies. Acta Neuropathologica Communications 7(22) (2019)

²⁵ See a more extensive list on this company poster reference at the 2017 Annual Meeting of The American Neurological Association: <http://ir.ionispharma.com/static-files/4ab8c591-c51b-45e1-8b0d-ef83a46c0853>

²⁶ Katsinelos, et al. Cell Reports 23, p2039–2055 (2018)

²⁷ Preclinical studies have shown that tau has different oligomer states before forming fibrils. See Takashima, A. Tauopathies and tau oligomers. J Alzheimer's Disease 37(3) p565-85 (2013)

²⁸ Schirmer R., et al. "Lest we forget you--methylene blue...". Neurobiology of Aging 32(12) p2325 (2011)

²⁹ Devos SL, et al., Tau Reduction Prevents Neuronal Loss and Reverses Pathological Tau Deposition and Seeding in Mice with Tauopathy, Sci Translational Medicine 25(9) 374 (2017)

Strategy #3 – Regeneration of Neurons

Neurotrophic factors, such as nerve growth factor (NGF), have been shown to regenerate and/or restore neuron function. Three clinical-stage programs are using direct formulations of NGF itself. Another drug candidate activates hepatocyte growth factor (HGF) to stimulate regeneration, while a fifth therapeutic in this sub-group is a truncated version of motoneuronotrophic factor (MNTF), which is believed to work on a broad range of receptors to promote neuronal survival. Four of these five programs are in Phase I, as shown in **Figure 2c**.

Three additional Phase II drug programs aim to regenerate neurons through different mechanisms. One drug candidate acts on sigma-1 receptors with high affinity, functioning as a neurotrophic and neuroprotectant.³⁰ Another Phase II program in this sub group is an extract from mastic gum (*Pistacia lentiscus*) believed to promote neuro regeneration. This is one of the few drugs in the Alzheimer's disease pipeline without a specific target. Lastly, a blood plasma fraction from young donors, containing a mixture of proteins and possibly growth factors known to regenerate neurons, was included in the neuro-regeneration category.

Four cell therapies are also included in this approach as they can supply neurotrophic factors or can be used to replace dysfunctional neurons. These clinical-stage cell therapies are created from adult human bone marrow mesenchymal stem cells (MSCs, n=2), placenta-derived stem cells (n=1), and adipose-derived stem cells (n=1).

Strategy #4 – Reversing Neuroinflammation

Over the last decade, significant evidence supports a strong inflammatory contribution to the etiology of Alzheimer's disease.³¹ There are currently seven drug programs directly targeting inflammatory processes. Interestingly, none of the molecular targets in these programs target the same inflammatory signaling pathways.

Three anti-inflammatory drugs target cytokine signaling, release, or overall dampening of cytokine effects on microglial cells, mast cells, or macrophages, for example, by targeting signaling kinases in the TNF or other inflammatory pathways. Another four drugs work by inhibiting activation or recruitment of microglia cells or macrophages, resulting in an overall decrease in neuroinflammation.

Strategy #5 – Targeting Epigenetic Modification

Post translation modification of DNA binding proteins may also play a role in the regulation of genes involved in many of the pathways discussed above.^{32,33} For example, sequencing the brains of Alzheimer's disease patients has revealed highly acetylated histones binding to areas of the genome associated with amyloid processing and clearance.³⁴ Once acetylated or methylated, histones in promoter regions may reduce or enhance gene expression. Histone methyltransferase and acetyltransferase (HMTs and HATs) are responsible for adding extra carbons to histones, whereas histone deacetylases and demethylases (HDACs and HDMs) remove them. Thus, all four histone modifying enzymes types could be drug targets within the epigenetic approach.

The current clinical pipeline contains three epigenetic programs. One targets a specific HDM, and simultaneously, monoamine oxidase. In preclinical studies, the drug candidates reduced memory loss and neuroinflammation.³⁵ A second clinical program is a combination drug, containing a pan HDAC inhibitor plus a bile acid that may serve as a mitochondrial membrane protectant. There is preclinical evidence showing histone deacetylase inhibitors can reverse Alzheimer's disease in mouse models.³⁶ Lastly, there is a drug in Phase I targeting bromodomains, regional modules in chromatin-associated proteins and enzymes (such as HATs) that can bind acylated areas of histones.

³⁰ Yano, T., et.al. Sigma-1 receptor is a molecular target for novel neuroprotectant T-817MA. *Alzheimer's & Dementia*, 11(7) p861 (2015)

³¹ Glass, C., et.al. Mechanisms Underlying Inflammation in Neurodegeneration. *Cell* 140(6), p918-934 (2010) and McCaulley, M., et al. Alzheimer's Disease: Exploring the Role of Inflammation and Implications for Treatment. *Int J Alzheimer's Disease*, ID515248 p.1-10 (2015)

³² Fischer, A. Targeting histone-modifications in Alzheimer's disease. What is the evidence that this is a promising therapeutic avenue? *Neuropharmacology* 80 p95-102 (2014). (There are two main epigenetic regulatory systems that cells use to control gene expression without any change in the genes themselves: histone modifications described here, and direct DNA medication via methylation. In addition to the histone modifications described above, other modifications exist and could be the target for future epigenetic drug discovery: ADP-ribosylation, ubiquitination, citrullination, and phosphorylation.)

³³ Fischer, A., et al. Targeting histone-modifications in Alzheimer's disease. What is the evidence that this is a promising therapeutic avenue? *Neuropharmacology*, 80, p95-102 (2014)

³⁴ Marzi, S. et al. A histone acetylome-wide association study of Alzheimer's disease: neuropathology associated regulatory variation in the human entorhinal cortex. *Nature Neuroscience*, 21(11), p1618-1627 (2018)

³⁵ Company press release (2018)

³⁶ Cuadrado-Tejedor, M., et al. A First-in-Class Small-Molecule that Acts as a Dual Inhibitor of HDAC and PDE5 and that Rescues Hippocampal Synaptic Impairment in Alzheimer's Disease Mice. *Neuropsychopharmacology*, 42(2) p.524-539. (2017)

Strategy #6 – Targeting Metabolic Pathways

Glucose and ketones are essential for energy utilization in the brain. Dysfunctional glucose or ketone metabolism has been correlated with neurodegeneration and could be a precursor to other pathologies such as inflammation, protein plaque buildup, and oxidative stress.

Two drugs in Phase II approach the glucose utilization issue in the context of Alzheimer's disease. One drug does this by selectively agonizing PPAR delta, a key nuclear receptor that regulates genes involved in glucose energy expenditure and other metabolically pathways. The other program is a delivery system for insulin that may increase brain exposure to the peptide. A third drug in development using a metabolic strategy for treating Alzheimer's is a purified fatty acid that can be converted to ketone bodies and thus used as an alternative energy source for brain cells with defective glucose metabolism.

Strategy #7 – Targeting Glucocorticoids

High levels of glucocorticoids over long periods of time have been linked to cognitive decline.³⁷ Studies have shown a strong association between plasma cortisol levels and amyloid β levels.³⁸ One strategy employed by drug developers to address this imbalance has been to block cortisol production in the brain. Two clinical-stage drugs do this through inhibiting a key enzyme involved in cortisol synthesis, 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1).³⁹

Strategy #8 – Targeting Oxidative Stress

The human brain consumes a large portion of the total oxygen inhaled, with 98% of it used by the mitochondria for energy production. However, some of the remaining 2% can lead to reactive oxygen species (ROS) that, if misregulated in the aging brain, can lead to unstable forms of free radicals. The imbalance of natural antioxidant mechanisms has been shown to play a vital role in the pathophysiology of neurodegenerative diseases, as excessive generation of ROS can lead to direct, lipid, protein, and DNA damage.⁴⁰

There is currently one drug candidate in Phase I targeting ROS through inhibition of microsomal prostaglandin E2 synthase-1. Preclinical work with this compound showed a suppression of neuronal loss in mice models of Alzheimer's disease.⁴¹

Strategy #9 – Targeting Infectious Agents

Bacteria and viruses can enter then brain and either inflict direct damage or elicit an immune response that could itself impose damage to neurons or neighboring cells. There is only one clinical-stage product being tested that targets infectious agents, an antibacterial drug. Preclinical evidence shows a correlation between periodontal (gum) disease caused by certain bacteria and Alzheimer's disease.

Strategy #10 – Targeting the Epichaperome

A more recent hypothesis behind the cause of neuron malfunction is the dysregulation of the epichaperome, a protein complex made of molecular chaperones and other co- factors. There are now more than 300 chaperones and co- factors known to associate with the epichaperome complex, expanding the target universe for this approach.⁴² As the chaperome system plays a role in disaggregating proteins, one of the primary correlating factors found in Alzheimer's patients, it has been the subject of drug research. Currently, there is one epichaperome drug in Phase I. Preclinical studies with the drug demonstrated tau reduction.

³⁷ J. Neuroscience. 26(35) p9047–9056 (2006)

³⁸ Pietrzak, P., et al. Plasma Cortisol, Brain Amyloid- β , and Cognitive Decline in Preclinical Alzheimer's Disease: A 6-Year Prospective Cohort Study Biological Psychiatry: CNNI 2 p45–52 (2017)

³⁹ Sooy K., et al. Cognitive and Disease-Modifying Effects of 11 β -HSD Type 1 Inhibition in Male Tg2576 Mice. Endocrinology, 156(12) p4592–603 (2015)

⁴⁰ Hueng, W., et al. Role of oxidative stress in Alzheimer's disease. Biomed Rep. 4(5) p519–522 (2016)

⁴¹ Baek, I., et al. AAD-2004 Attenuates Progressive Neuronal Loss in the Brain of Tg-betaCTF99/B6 Mouse Model of Alzheimer Disease. Exp Neurobiology 22(1) p31–37 (2013)

⁴² Joshi, S. et al. Adapting to stress — Chaperome networks in cancer. Nature Reviews Cancer, 18 p562–575 (2018)

Modalities in the Clinical-Stage Pipeline

Modalities under development for disease-modifying Alzheimer's programs are weighted toward small molecules, at 53% of the pipeline, as shown in **Figure 3**. Although this makes intuitive sense as small drugs can be designed with greater accessibility to regions of the brain enclosed by the blood brain barrier, it should be noted that more than half of the overall industry pipeline is comprised of small molecules. Almost a third of the drugs in the Alzheimer's clinical pipeline are proteins (such as antibodies or smaller peptides). There are four cell-based therapies and one antisense drug. The eight vaccines in the clinical pipeline are split between cell-based (n=4) and peptide-based (n=4).

2019 ALZHEIMER'S DISEASE PIPELINE BY MODALITY

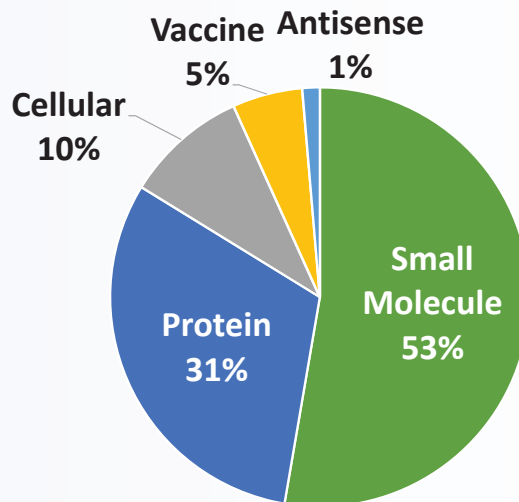


Figure 3. Breakdown of modalities in the current disease-modifying Alzheimer's disease clinical pipeline.

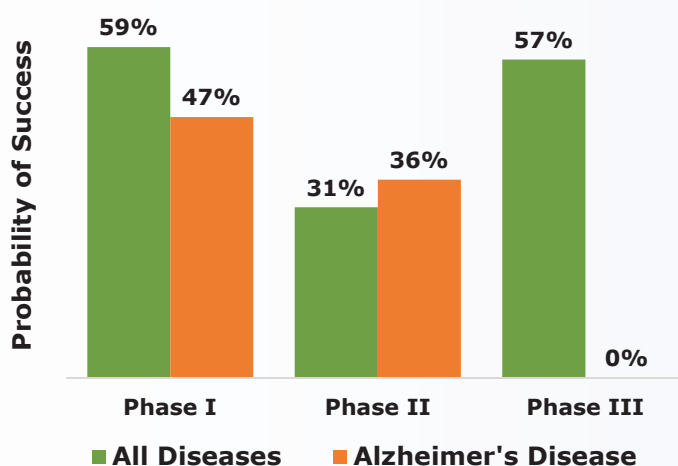
Preclinical Pipeline

To predict what may enter the clinical pipeline soon, we examined novel preclinical disease-modifying Alzheimer's disease programs in the Biomedtracker databases and recently published literature. We found that 23 of the 102 preclinical programs listed had unique targets not currently in the clinic, indicating further advances may be on the horizon. The mechanistic strategies are quite varied within the 23 new targets, including caspases, different growth receptors, inflammation factors, kinases, and modified blood proteins that may restore or protect neuronal function. Sixteen of the preclinical programs had unknown mechanisms.

Clinical Development Success Rates for Novel Alzheimer's Disease Drug Programs

The clinical trial success rates for Alzheimer's disease drug candidates were found to be lower than what is observed across all disease areas combined, except for those Alzheimer's disease therapies that advance to Phase II. Based on data obtained from the Biomedtracker database and annotating for disease-modifying programs only, 139 advanced or suspended programs were analyzed over the period January 2008 through January 2019.⁴³ As shown in **Figure 4**, no disease-modifying Alzheimer's drug development program has been successful in Phase III. Drug development programs in Phase I had a 47% chance of transitioning to Phase II, vs. the industry average of 59%. However, the chance of transitioning to Phase III was higher than the industry average: 36% chance of transitioning from Phase II to Phase III vs. 31% for all diseases.

CLINICAL DEVELOPMENT SUCCESS RATES FOR ALZHEIMER'S DISEASE DRUGS 2008-2019



Strategy	Phase of Program Suspension			Total
	Phase I	Phase II	Phase III	
Amyloid pathway	30	13	9	52
Tau pathway	4	2	0	6
Neuroinflammation	3	2	2	7
Metabolic pathway	2	2	2	6
Neuro-regeneration	0	4	1	5
Antioxidant	1	2	1	4
Glucocorticoid	0	3	1	4
Calcium channels	0	1	1	2
Unknown	1	0	0	1
Total	41	29	17	87

Figure 4. Clinical success rates for all Alzheimer's disease indications compared to success rates for all other disease areas combined, January 2008 through February 2019. Data for Alzheimer's Disease is based on approximately 139 drug program transitions in the Biomedtracker database. Right: Suspended programs since 2008 are listed by phase and the strategy pursued for the failed drug program. Under glucocorticoids, although this is primarily cortisol targeting in the current pipeline, we include neurosteroids (such as DHEA derivatives) in this category.

⁴³ Prior study on success rates, (Thomas, D., et al. BIO, BioMedtracker, Amplion. Clinical Development Success Rates 2006-2015 (2016)) can be accessed at www.bio.org/iareports, showed success rates from Phase I to approval at 9.6% for all diseases.

Analyzing clinical programs that were active at any point during January 2008 to February 2019, we found 87 suspended clinical programs. Note that this is different from individual clinical trial failures and encompasses complete program shut downs. This is significant for Alzheimer's R&D because individual drugs can fail late-stage dementia and move to mild or moderate, or even "Preclinical" stage (pre-dementia) clinical trials, adding to the total development cost and time. Indeed, some currently active programs have failed multiple trials but are not yet suspended. This indicates that the number of trial failures is much higher than suspensions over the time period examined.

Examples of failed programs within individual strategies are numerous, but many strategies continue to be pursued even after multiple failed programs. In the case of the amyloid strategy, although 52 suspensions have been recorded since January 2008, there are currently 33 clinical-stage amyloid targeted programs ongoing (**Figure 2a**). This illustrates both the conviction behind scientific evidence pointing to the role of amyloid in the disease pathogenesis, but also speaks to the number of ways to target the amyloid pathway as discussed above. For example, the antibody approach for binding amyloid has multiple epitopes and conformational states that can be targeted, possibly with varying impacts on the disease.⁴⁴ Within the 52 suspended amyloid programs, eight have failed in Phase III, suggesting a significant amount of investment dollars consumed by these efforts as Alzheimer's trials for Phase III programs tend to be relatively large (compared to cancer Phase III studies for example).

In addition, different modalities, from small molecules to nucleic acid-based drugs and cell therapies, can be tested for a single target. For example, 14 small molecules targeting beta or gamma secretase are found within the suspended amyloid program list. Although this certainly does not support the preclinical evidence behind shutting down or altering APP processing, other routes of slowing APP may be physiologically more conducive to the final objective of showing clinical benefit, and thus we cannot rule out this strategy.

There is only one suspended strategy in the time period studied that is no longer in clinical development: The Calcium channel hypothesis. One of these was a repurposed drug program of an approved calcium channel blocker approved for treating hypertension. Like other repurposed drugs in Alzheimer's, although showing hints of activity in preclinical models (even anti-inflammatory and anti-tau activity) this program did not succeed in late-stage studies. A novel calcium channel blocker also failed at Phase IIb.

Certain sub-strategies are now no longer pursued after clinical development setbacks. For example, the "metal ion hypothesis" is no longer in the current clinical pipeline. Metals (iron, copper, manganese, aluminum, and zinc) could serve as beneficial antioxidants as cofactors in metalloproteins involved in neuronal metabolism. However, they have also been proven in the laboratory setting to have negative effects such as binding to amyloid directly and facilitating accumulation. In clinical practice, removing excess metal ions has not shown significant benefit. Regardless, there are still supporters of this hypothesis.⁴⁵

Other targets that were suspended but not in the current clinical pipeline include RAGE, NFKB, RIPK1, Lp-PLA2, GnRH receptors, GDNF, casein kinase, glycogen synthase kinase (GSK), HMG CoA reductase, eicosanoids, mTOT, and calpain. Targets with suspended histories but still under clinical investigation include amyloid and tau pathways, microtubules, sigma receptors, NGF, 11 β -HSD, and PPAR.

⁴⁴ Panza, F., et al. A critical appraisal of amyloid- β -targeting therapies for Alzheimer disease. *Nature Reviews Neurology*, 15 p73-88 (2019)

⁴⁵ Mirza A, et al. Aluminum in brain tissue in familial Alzheimer's disease. *J Trace Elem Med Biol*. 40 p30-36 (2017)

Trends in Venture Investment and Clinical Trial Initiations in Alzheimer's Disease

We calculated venture funding for private companies with lead compounds in Alzheimer's Disease for each year over the last decade. A more comprehensive method for assessing investment across the industry, based on quantifying the number of clinical trials starts, is also presented below.

2008-2017 VENTURE INVESTMENT INTO U.S. COMPANIES WITH LEAD NOVEL DRUG PROGRAMS IN ONCOLOGY VS. ALZHEIMER'S DISEASE

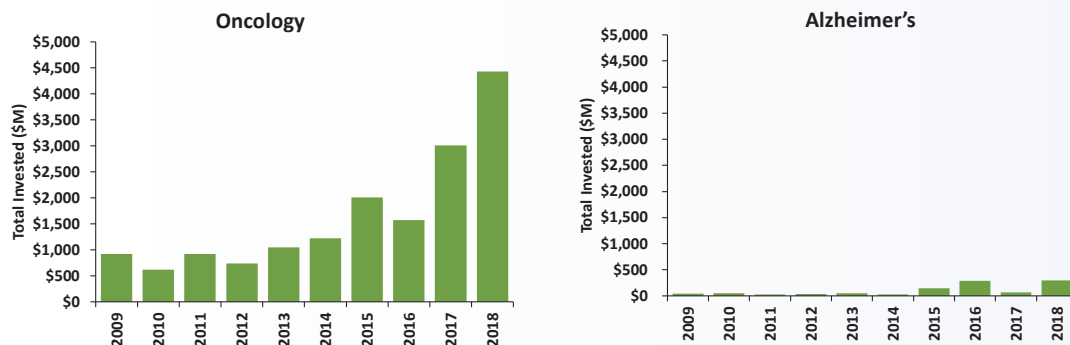


Figure 5. Left: Venture funding of companies with lead products in oncology, 2009-2018. Right: Venture funding of companies with lead products in Alzheimer's disease, 2009-2018.

As can be seen in **Figure 5**, venture investment into U.S. companies with lead Alzheimer's disease programs from 2008 to 2017 totaled \$741 million. This is 16 times less than the funding received for novel oncology drugs (\$12.2 billion) during the period from 2008 to 2017. Nine companies with lead Alzheimer's disease drugs were financed each year, on average. By comparison, there were 79 oncology companies financed each year, on average, suggesting that early-stage investors currently prioritize other disease areas, such as oncology, over Alzheimer's disease.

The above methodology, whereby lead asset is used as a proxy for private investment, tends to underestimate venture dollars ultimately used for Alzheimer's disease R&D in small companies. Although most capital will tend to be used for the lead asset, this is not always the case, and precise data on internal R&D spending per project is not available. Thus, some companies with lead drugs in Parkinson's, ALS, and other related neurologic diseases may in fact have earlier stage programs in Alzheimer's disease. Using the broader Neurology disease area excluding pain, we still get \$3.4 billion for Neurological diseases versus \$12.2 billion for cancer.

We also use a method for approximating broader industry R&D investment activity (combining small, midsize, and large public companies and private biopharmaceutical companies) and the annual level of funding for private emerging biotech companies. This requires the use of the TrialTrove database, which tracks clinical trial start dates by indication. From 862 Alzheimer's trial starts, we categorized trials for novel drugs, vs. nonintervention trials, reformulations, combinations of older drugs and other duplicate trials per phase, identifying 170 novel drug intervention trial starts over the 10-year period.

2008-2017 CLINICAL TRIAL STARTS FOR ALZHEIMER'S DISEASE DRUG INTERVENTION TRIALS

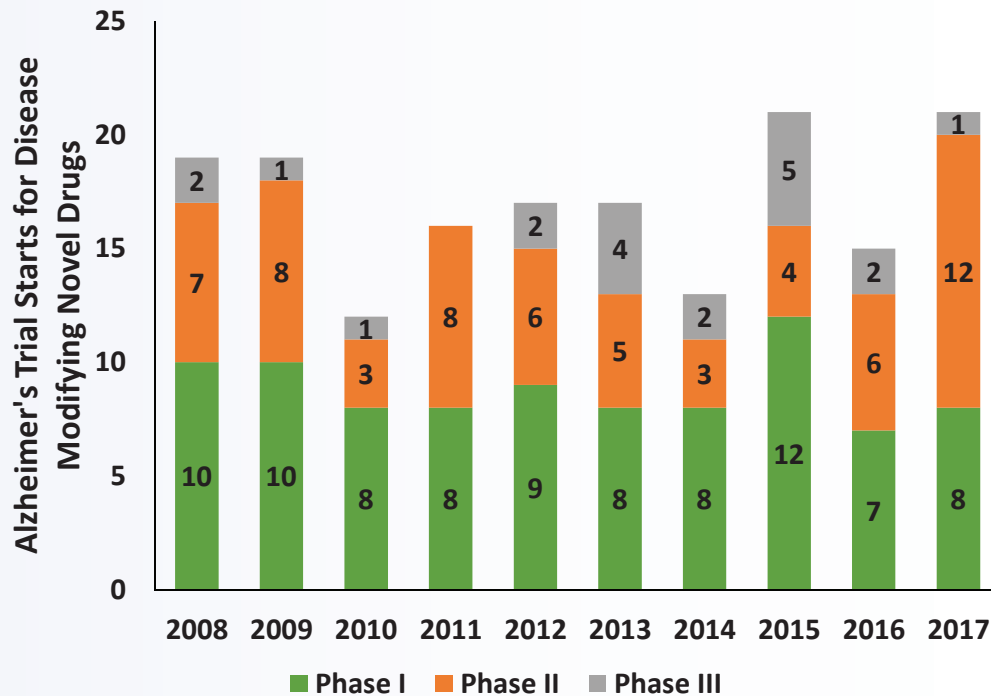


Figure 6. Clinical trial starts for novel drugs for Alzheimer's disease, 2008-2017. TrialTrove data accessed October 2018. A total of 862 clinical trial starts were retrieved from TrialTrove. Trials were individually assessed for disease modifying vs. symptom modifying drugs and trial phase cohorts de-duplicated. A total of 170 novel drug intervention trials were initiated during this time period.

As shown in **Figure 6**, clinical trial starts involving potential disease modifying Alzheimer's disease drugs remained in a range of 11-21 starts per year, with the average being 17, over the last decade. Two of the highest years of trial initiation were in 2015 and 2017, with the two lowest years in 2010 and 2014.

Trials were also grouped by phase in **Figure 6**. Phase I trial initiations for disease modifying drugs have been constant over the last decade, but low in volume (ranging from 7-12 per year). Phase II and Phase III trial starts have been less consistent, ranging from 3-12 and 0-5 per year, with no detectable trend.

Discussion

Alzheimer's disease in elderly populations of both developed and developing nations is growing. Along with the hardship of caring for patients, the staggering economic costs that nations will be facing over the next few decades are unprecedented. Solving for this coming crisis should be front and center of policy initiatives aimed at reducing future economic societal burden. It is likely that the hope for change comes in the form of therapeutic interventions to stop the progression of this disease, but this will require a fully functional, seamless ecosystem of regulators, industry, patients and academia.

Unfortunately, to date there has yet to be a disease-modifying pivotal program that has transitioned to NDA/BLA filing. In the current clinical-stage pipeline we found 74 drug programs with disease-modifying potential for Alzheimer's in Phase I-III. This compares to a report published by Cummings, J., et al. that found 70 disease-modifying therapies in the January 2018 pipeline.⁴⁶ This total number remains below the number of novel clinical programs in a single sub-indication for oncology. For example, breast cancer has 158 active, novel clinical development programs, lung cancer has 180, and leukemias have 211 – each well above the total of 74 found in the Alzheimer's disease clinical pipeline for disease-modifying agents.⁴⁷

Although there could be more shots on goal, the fact that there are 10 differentiated approaches and more than 30 molecular targets in the clinic, offers hope. To deliver on these and beat historical odds, creative solutions are required during the development lifespan. Coordinated dialogue between stakeholders will help optimize development programs that aim to make meaningful differences in patient's lives. For example, academic and industry findings have helped inform the recent modernization of the FDA's endpoint guidelines in Alzheimer's trials.⁴⁸ As our scientific understanding of the disease evolves, so must the way we develop drugs. Policies supporting efficient and effective regulatory environments will encourage investments into new treatments. For example, expanded utilization of biomarkers to stratify patient populations to better predict what treatments work best, and when and for whom they work best, would serve to incentivize innovation and change the paradigm of how we treat this widespread disease.

Meanwhile, more effort upstream is still needed. Continued funding of basic research to advance our understanding of the biology of Alzheimer's disease will arm drug developers with new targets and approaches to attack this complex disease. Although we now have identified multiple players in the etiology of the disease, the exact detailed molecular mechanism behind Alzheimer's remains unknown. Many therapies found to be very effective in animal models, and even some with promising Phase II results, have failed to show significant effects in statistically rigorous trials. To find the right intervention may require more predictive animal models and more advanced biomarkers. Although a few biomarkers for Alzheimer's have been established, such as the CSF measurement for amyloid and tau, or via PET scans with tracer agents, more biomarkers for early-stages of the disease are needed.^{49,50}

All of this will require more funding. Fortunately, there has been a substantial increase in government funding for Alzheimer's research in recent years. The U.S. National Institute of Health has seen a tripling of its budget from Congress over the last three years for Alzheimer's and related dementias. Much of this increase, to \$1.9 billion in 2018, is for exploratory research grants funded via the National Institute on Aging (NIA).⁵¹ A few venture capital-backed Alzheimer's focused start-ups have also launched in the last few years. Although dwarfed by levels seen in oncology (by 16x), the venture funding trend is upward and small emerging companies now account for 77% of all Alzheimer's clinical programs. Other sources for basic research funding are also trending up. For example, The Bill and Melinda Gates Foundation and other family office investors have recently added \$30M to the Alzheimer's Drug Discovery Foundation, while the American Association of Retired Persons (AARP) has recently added \$60 million to the Dementia Discovery Fund.⁵²

The Biotechnology Innovation Organization (BIO) and member companies view innovation as the key to helping patients with Alzheimer's disease. Advancements in science, more choices for patients, and a policy environment that stimulates investment in R&D are necessary to achieve this goal.

⁴⁶ Cummings, J., et al. Alzheimer's disease drug development pipeline: 2018. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* 4 p195-214 (2018)

⁴⁷ Data for oncology R&D pipeline is taken from the Biomedtracker database, NMEs and novel biologics only, and current as of January 2019. A total count by disease area can be found in Thomas, D., Wessel, C. BIO Industry Analysis. *Emerging Company Trend Report*, (2018) (www.bio.org/iareports)

⁴⁸ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596728.pdf>

⁴⁹ Aisen, P., Cummings, J., et al. On the path to 2025: understanding the Alzheimer's disease continuum. *Alzheimer's Research & Therapy*, 9 (60) (2017).

⁵⁰ <https://www.scientificamerican.com/article/better-biomarkers-could-help-us-treat-alzheimers/>

⁵¹ <https://www.sciencemag.org/news/2018/08/alzheimer-s-gamble-nih-tries-turn-billions-new-funding-treatment-deadly-brain-disease>

⁵² <https://www.aarp.org/health/dementia/info-2018/aarp-investment-dementia-alzheimers.html> and <https://www.gatesnotes.com/Health/A-better-way-of-diagnosing-Alzheimers> (accessed February 2019)

Appendix

Marketed Drugs for Alzheimer’s Disease

There are four active compounds on the market that treat symptoms of Alzheimer’s disease, such as mental alertness and depression. However, as of this writing, there are no disease-modifying therapeutics FDA approved for Alzheimer’s disease. Three of the four active substances marketed for Alzheimer’s are cholinesterase inhibitors that work primarily through stabilizing the acetylcholine neurotransmitter levels by slowing its breakdown. It has been known for more than 30 years that a breakdown in highly cholinergic neurons is associated with Alzheimer’s. Numerous drugs have been in development targeting choline acetyltransferase or acetylcholinesterase under this “Cholinergic Hypothesis”, but they have not been as useful in earlier stages of the disease. The fourth compound marketed (memantine) is an N-methyl-D-aspartate (NMDA) antagonist which acts to block overactive functioning, or toxicities, related to of the neurotransmitter glutamate.

Clinical-stage drug programs with symptom-modifying potential in Alzheimer’s disease.

SYMPTOM-MODIFYING CLINICAL PIPELINE FOR ALZHEIMER’S

Strategy	Phase I	Phase II	Phase III	Total
Acetylcholine	9	4	1	14
Monoamine	4	4	4	12
Glutamate	3	1	0	4
Synaptic function	3	2	0	5
Cannabinoid receptors	0	2	0	2
GABA	0	1	0	1
Glutamine	1	0	1	2
Circadian	0	2	0	2
Unknown	4	0	0	4
Total:	24	16	6	46

TOTAL ALZHEIMER’S PIPELINE

Category	Phase I	Phase II	Phase III	Total
Symptom Modifying	24	16	6	46
Disease Modifying	27	34	13	74
Total:	51	50	19	120

A1. Clinical-stage drug programs with symptom-modifying potential in Alzheimer’s disease, as well as the total Alzheimer’s pipeline.

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