FALL 2018

RESEARCHING ALZHEIMER'S MEDICINES

SETBACKS AND STEPPING STONES

PhRMA
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Foreword

In recent years, a dearth of new treatments for Alzheimer's disease has left many to conclude that a cure is out of reach. As this report demonstrates, there's no doubt that setbacks are inevitable and instructive when tackling a complex disease like Alzheimer's. But given the increase in understanding of the disease in the past few years and the steady rise in Alzheimer's treatments in development, patients and their families have good reason to be optimistic.

In fact, a recent analysis of late stage Alzheimer's drugs, conducted by ResearchersAgainstAlzheimer's, a global network of leading researchers, found nearly a hundred treatments in Phase 2 and 3 development in 2018. The analysis demonstrates that the drugs in development are increasingly attacking the disease in different ways – an important fact given that successful future treatments will likely rely on multiple therapies to stop the disease.

And yet despite the diversity of treatments in development, there is a shortage of geriatricians to care for the country's aging population, patients are commonly misdiagnosed, there continue to be long wait times to see neurologists, racial disparities persist, and many patients are never told of their diagnosis by their doctor. Additionally, primary care practices are not equipped, trained, or incented to build brain health practices into routine standards of care. This lack of preparation and training has led to a shortage of treatments for cognitive impairment, an oversight of potential risk reducing behaviors, and often late and inaccurate diagnosis of Alzheimer's.

These signs all indicate that the U.S. healthcare system may not be prepared to administer novel treatments to patients when they become available. As the science progresses, physicians, lawmakers, advocates, and industry leaders must work together to ensure we're all ready for life-saving treatments.

From polio to HIV/AIDS, past global health efforts have taught us that we can successfully tackle challenging healthcare issues if we are focused and collaborative. And at a time when the global impact of Alzheimer's is sharply rising, it's now more important than ever that the Alzheimer's community – including researchers and advocates – come together to accelerate a cure.

As millions of patients and their families in the U.S. and abroad continue to hold out hope for a cure, time is of the essence. We shouldn't waste another minute.

Sincerely,

George Vradenburg
Co-Founder and Chairman
UsAgainstAlzheimer's

UsAgainst Alzheimer's

Executive Summary

Alzheimer's disease is a devastating illness that gradually robs a person of everything they hold dear: their memories, their relationships, their personality, their independence, and, ultimately, their life. Family and caregivers face many challenges as they care for a loved one who is gradually slipping away. Alzheimer's also places a significant burden on the health care system at-large. As the aging population expands, so does the need to address and conquer Alzheimer's disease. Without progress, the cost and resource burden of Alzheimer's will continue to grow, and countless individuals and families will be impacted.

To treat, slow, and prevent Alzheimer's disease, new treatments are urgently needed. Biopharmaceutical research companies are studying many potential new treatments. However, the path from basic research to the development of new medicines is extremely long and complex with many setbacks along the way. This is particularly true in the case of Alzheimer's disease, where diagnosis is challenging, and we lack a full understanding of the disease.

A new analysis finds that between 1998 and 2017, there were **146 unsuccessful attempts** to develop medicines to treat and potentially prevent Alzheimer's. In that same timeframe, only four new medicines were approved to treat the symptoms of Alzheimer's disease. In other words, for every research project that succeeded, about 37 failed to yield a new medicine.

Although these setbacks are deeply disappointing, they provide critical data that inform future research efforts. Medical research is often iterative, with breakthroughs rarely happening overnight. In fact, lessons learned from unsuccessful projects help inform potential new scientific avenues to explore in future research efforts. Progress in Alzheimer's drug development will undoubtedly be the result of successes informed by setbacks.

That said, as critical as setbacks are to researchers, they are nonetheless costly and illustrate the long and arduous process of developing medicines for diseases as complex as Alzheimer's. Recognizing the risk and significant scientific uncertainties involved in Alzheimer's research and the urgent need for progress, it is imperative that we have a policy and regulatory framework that supports a robust research enterprise and encourages innovators to take risks and accept the inevitable setbacks.

Biopharmaceutical researchers and the companies they work for are profoundly committed to leveraging the promise of our expanding scientific knowledge to find treatments that halt or prevent Alzheimer's. Companies are currently working on **92 medicines for the treatment of Alzheimer's and other dementias**, giving current and future patients and their families hope for a future free of this devastating disease.

> "Despite the difficulties and setbacks that the field has experienced in Alzheimer's drug development, with perseverance, we can illuminate the complexities of this disease and eventually find a disease-modifying medicine."
>
> **George Vradenburg, Chairman at UsAgainstAlzheimer's[1]**

Introduction

Alzheimer's disease is the most common cause of dementia resulting in significant problems with memory, thinking, and behavior. It is a growing health care burden of epidemic proportions. Despite significant effort and investment, the quest to develop an effective disease-modifying medicine to treat or prevent this devastating and complex disease has resulted in many failures.

Developing new medicines is critical to tackling Alzheimer's disease, but the process of bringing innovative therapies from an early idea to patients is as complex as the disease itself. What many do not realize is that behind every medicine that makes it to patients, there are many more that did not. In fact, across all diseases, only 12 percent of drugs that enter clinical trials will eventually reach approval.[2]

While these setbacks are inevitable and disheartening for patients and researchers alike, they can lead to new learnings that advance our research efforts going forward.

This report highlights the burden of Alzheimer's disease, the unique challenges of developing medicines to treat or slow its progression, and the setbacks and advances that have occurred as a result of our efforts to conquer this devastating and increasingly costly illness.

> "There's a revolution underway in the Alzheimer's research world. At the heart is a change in the way researchers and regulators define and stage the disease, and it might just lead to the breakthrough Alzheimer's researchers, patients and families have been waiting for."
>
> **Gary Tong, US Therapeutic Area Head, Dementia at Lundbeck[3]**

The Impact of Alzheimer's Disease: Patients, Society, the Economy

Alzheimer's disease gradually robs a person of everything they hold dear: their memories, their relationships, their personality, their independence, and, ultimately, their life. Many of us know someone — a grandparent, a friend, or loved one — who has been diagnosed with this debilitating disease. We have seen their symptoms progressively worsen over time to the point where they require around-the-clock care and may eventually succumb to the disease.

According to the Alzheimer's Association, about 5.7 million Americans are currently affected by Alzheimer's dementia, the symptomatic phase of the disease.[4] Today, it is the sixth leading cause of death in the United States, although studies suggest that Alzheimer's deaths are underreported.[5]

Alzheimer's also places a significant burden on the health care system at-large. Currently, Alzheimer's disease and other dementias account for $277 billion each year in direct medical costs.[6]

SOCIETY'S GREAT CHALLENGE[7]

5.7 MILLION
Americans impacted

6TH LEADING
cause of death in the U.S.

$277 BILLION
each year in direct medical costs

16.1 MILLION
caregivers providing **$232.1 billion in uncompensated care**

1 IN EVERY 5 MEDICARE DOLLARS
goes towards care for patients with Alzheimer's dementia[8]

> "The prospect of being able to offer meaningful disease-modifying therapies to individuals suffering from this terrible disease is both exciting and humbling."
>
> **Alfred Sandrock, Executive Vice President and Chief Medical Officer at Biogen[17]**

Adding to the challenges of Alzheimer's is the uniquely significant toll it takes on a patient's family and friends, who are often required to step in as caregivers. As a result, the indirect costs of the disease are enormous: nearly 18.4 billion hours of uncompensated care were provided by an estimated 16.1 million caregivers in 2017 — valued at approximately $232.1 billion.[9] This figure does not include the lost productivity of caregivers who must leave the workforce to care for a loved one.

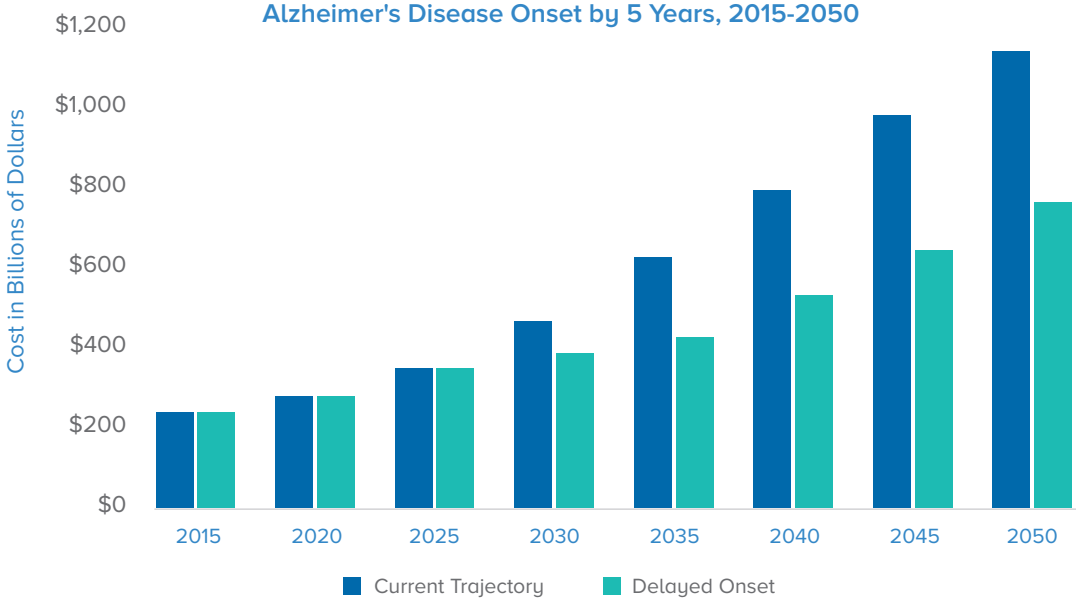
The impact of Alzheimer's disease on spending in the Medicare program is especially pronounced. In 2018, Medicare is projected to spend $140 billion on treating patients with Alzheimer's and other dementias.[10] This equates to about one in every five Medicare dollars being spent on Alzheimer's.[11]

Often overlooked is Alzheimer's disproportionate impact on communities of color. In fact, African Americans are two times more likely and Latinos are one and a half times more likely to develop Alzheimer's than non-Hispanic white Americans. Despite this higher prevalence, African Americans and Latinos are, on average, less likely than white Americans to be diagnosed with Alzheimer's by a health care professional.[12]

Looking ahead, projected costs of this disease are expected to grow exponentially as the patient population continues to rise. Without a disease-modifying treatment, experts predict the number of Americans with Alzheimer's could reach a total of 13.8 million patients by 2050.[13] As a result, the direct costs of Alzheimer's disease will likely balloon to $1.1 trillion by that same year.[14]

New disease-modifying treatments, however, could dramatically reduce the projected economic and societal burden of Alzheimer's. According to the Alzheimer's Association, if a new treatment that delays the onset of Alzheimer's by five years is approved by 2025, the number of people in the U.S. with the disease could be reduced by approximately 40 percent.[15] The development of such a treatment could save an estimated $367 billion a year by 2050 (See chart below).[16]

Projected Impact of a Medicine that Delays Alzheimer's Disease Onset by 5 Years, 2015-2050



Source: Alzheimer's Association, "Changing the Trajectory of Alzheimer's Disease: How a Treatment by 2025 Saves Lives and Dollars," May 2015, https://www.alz.org/media/Documents/changing-the-trajectory-r.pdf

Our Current Understanding of Alzheimer's

While many of the biological causes and underpinnings of Alzheimer's remain a mystery, our understanding of many aspects of the disease, including potential ways to detect, attack or prevent it, has advanced in recent years.

Molecular and Genetic Underpinnings

Research to date shows that there are two hallmarks of Alzheimer's disease: the accumulation of amyloid protein in the brain and the formation of tangled bundles of fibers within brain cells (neurons).[18]

Many individuals with Alzheimer's present with an abnormal build-up of fragments of a protein called *beta-amyloid*, referred to as "plaques." These plaques tend to accumulate in the spaces between neurons. Another characteristic of Alzheimer's is the development of "neurofibrillary tangles," or clumped, twisted masses of protein fibers. These fibers consist of a protein called *tau*.[19,20] The protein plays a key role in the formation of microtubules, structural components of brain cells that help transport nutrients and provide cell structure. Both of these changes often take place in regions of the brain that support memory and can lead to neuron damage and death — potentially contributing to the memory loss that is seen among Alzheimer's patients.

While researchers have enhanced their understanding of the molecular changes characterizing Alzheimer's, numerous questions remain.[21,22] For example, it is unclear whether the development of amyloid plaques and tau tangles are causes or symptoms of the disease.[23]

Scientists believe some of these molecular changes may have a genetic component. An estimated 1 percent or less of Alzheimer's cases develop as a result of mutations to any of three specific genes involving the amyloid precursor protein (APP) and the genes for two additional proteins, called presenilin 1 and 2. Individuals that inherit specific mutations in either the APP or presenilin 1 genes are guaranteed to develop the disease while those with a mutation in the presenilin 2 gene have a 95 percent chance of developing the disease.[24] Mutations in other genes and the extra copy of chromosome 21, which characterizes Down syndrome, are other less common genetic changes that may affect one's risk of Alzheimer's.[25]

In combination with genetic factors, environmental and lifestyle factors are also believed to contribute to Alzheimer's disease. Studies have shown that regular physical activity and management of chronic diseases, such as diabetes, obesity, and hypertension, may reduce the risk of cognitive decline and dementia.

Reflecting the complexities of neurological diseases, much of the biology behind Alzheimer's disease is unknown. However, scientists continue to gain insights that may inform new ways of diagnosing, preventing, and treating this disease.

Diagnosis and Treatment Options

Alzheimer's disease develops well before patients develop the symptoms associated with Alzheimer's dementia. In fact, research suggests that brain changes associated with the disease may begin 20 or more years before symptoms appear.[26,27,28,29] Clinicians are increasingly using biomarkers – a biological characteristic that is objectively measured and evaluated as an indicator of disease – to help diagnose patients in clinical practice and identify patients to participate in clinical trials, although more

> "The more accurately we can characterize the specific disease process pathologically defined as Alzheimer's disease, the better our chances of intervening at any point in this continuum, from preventing Alzheimer's to delaying progression."
>
> **Richard Hodes, Director at the National Institute on Aging[30]**

are needed to better diagnose and monitor the disease.[31]

While there is no single test for Alzheimer's, physicians currently use a variety of tools to help diagnose the disease. Two imaging techniques include positron emission tomography (PET) and single-photo emission computed tomography (SPECT). PET is used in combination with various radioactive tracers to help visualize amyloid plaques and neurofibrillary tangles in the brain.[32] SPECT can help differentiate Alzheimer's disease from other brain conditions, such as depression.[33]

However, non-imaging biomarkers are needed to advance our capabilities to more easily monitor disease progression and response to treatment as well as improve the rigor and efficiency of clinical trials.[34] Potential non-imaging biomarkers include molecules measured in the blood, urine, cerebrospinal fluid, or other parts of the body. More advanced diagnostic tools could also aid in efforts to develop disease-modifying treatments for Alzheimer's, which remain elusive.

There are currently five Food and Drug Administration (FDA) approved medicines for Alzheimer's disease, all of which are used for symptom management by helping to maintain mental function and control behavioral symptoms.[35] Of the existing FDA approved medicines, most are used in the treatment of moderate to severe Alzheimer's and work to inhibit cholinesterase, which may help preserve memory and thinking.[36,37] Medicines used to treat moderate to severe Alzheimer's attempt to mitigate brain cell death.[38]

The development of innovative medicines to prevent or slow the onset and progression of Alzheimer's disease would have a profound impact on the lives of millions of people. Researchers across the country in biopharmaceutical companies, academia, and government are determined to develop such treatments.

Efforts to Advance Early Detection

Developing new ways to diagnose the disease will be critical to identifying patients in the early stages of Alzheimer's, and to ultimately provide them with treatments to prevent or delay disease progression. According to the Alzheimer's Association, advances in early detection capabilities could save the U.S. an estimated $7.9 trillion.[39]

Researchers are tirelessly searching for more simple and accurate biomarker tests for Alzheimer's. For example, in recent clinical trials, investigators used PET imaging and magnetic resonance imaging (MRI) as a way to confirm the diagnosis of the disease as well as to identify potential disease-modifying effects in research patients.[40] Other early detection studies focus on identifying biomarkers that indicate rising levels of beta-amyloid and tau in the brain, as well as neuron damage or deterioration.[41]

Investigators are simultaneously exploring early detection strategies targeting other potential biological pathways for Alzheimer's. For example, given research indicating that impaired glucose processing increases the risk of dementia, studies are using a combination of PET imaging and the radioactive tracer fluorodeoxyglucose to measure the amount of glucose metabolism in the brain.[42]

In addition to identifying patients for clinical trials, scientists believe that biomarkers will eventually be critical to identifying individuals with early-stage Alzheimer's and monitoring the effects of treatment.[43] Thus, as our ability to reliably diagnose the disease advances, so does our ability to develop effective treatments.

On the Front Lines

with Eric Karran, Vice President, Foundational Neuroscience Center at AbbVie

Q **What do we understand about the underlying causes of Alzheimer's?**

A What we believe is that a small protein called Abeta starts to deposit in the brain to form abnormal aggregates called plaques. That seems to be the first thing that occurs in the brain. And for reasons we don't fully understand, that provokes a response in the brain whereby another pathology called tau tangles forms in neurons and then spread throughout the brain. This starts in one part of the brain, called the entorhinal cortex, which is very important in memory consolidation and retrieval. But then it spreads throughout the brain ultimately causing the cognitive decrements that we see in Alzheimer's disease — loss of memory, loss of the ability to make decisions, and ultimately loss of language.

Q **What role does genetics play in Alzheimer's disease and how does that impact our research and the types of treatments that we are pursuing?**

A Genetics has been really important in Alzheimer's disease and a lot of this was worked out in the 1990s. What scientists discovered was that a single change to a gene called the amyloid precursor protein was able to initiate early Alzheimer's disease with 100 percent certainty. So, this was a very, very important clue that this process — which ultimately leads to the amyloid plaque — is critically important in Alzheimer's disease. And with that understanding, we were able to design animal models in species like the mouse that have some of the pathology of Alzheimer's disease. And in turn that has enabled us to test compounds and therapeutic approaches to either delay or clear the amyloid from the brain. These therapeutic approaches have been or are now being tested in human clinical studies.

Q **How has our understanding of complex neurodegenerative diseases evolved over the past years?**

A What's really changed is the recognition that the disease process starts very early on in people and it precedes the actual symptoms that they suffer from by about 10 to 20 years. This is incredibly important because it shows us that for medicines to be effective we need to find a way to treat people even before they present with clinical symptoms. And that has driven a whole lot of the science that we call biomarkers. These are things that you can measure that correlate with disease process. And we ultimately hope that we can measure some of these pathological processes going on in the human brain with imaging agents.

Challenges of Developing Alzheimer's Medicines

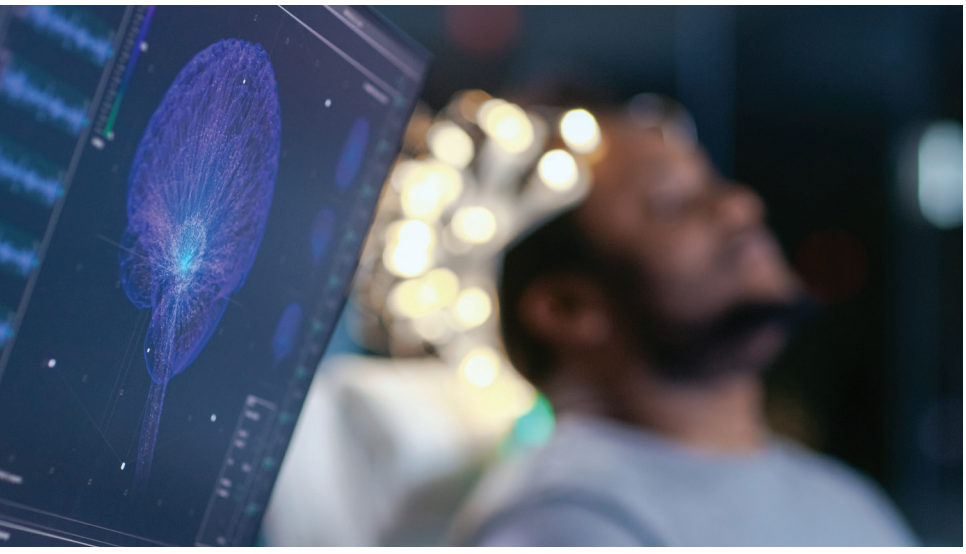
> "The lack of progress in the treatment and prevention of Alzheimer's disease is frustrating for patients, families, physicians, researchers, industry, funders, and policy makers. Understanding the causes for these failures is essential for informing future trials."
>
> **David A. Bennett, Physician at Rush Alzheimer's Disease Center[45]**

Despite the critical need, developing a medicine to prevent, delay, slow, or cure Alzheimer's disease is exceptionally difficult. Years of research have yielded only a handful of medicines providing partial symptomatic relief. Successful disease-modifying treatments continue to elude the research community for several reasons, including limitations of preclinical models, the absence of validated, non-invasive biomarkers, clinical trial challenges, and, above all, a significant gap in scientific knowledge.

Adding to these challenges, many researchers believe that no single medicine will be able to defeat Alzheimer's. Rather, several medicines will likely be needed to combat the disease.[44]

Significant Gap in Scientific Knowledge

Scientists still do not have a full understanding of the underlying causes and mechanisms of Alzheimer's disease. In fact, it is unknown whether many of the defining molecular characteristics of the disease are causes, effects, or signs of progression. This knowledge gap compounds the challenge of identification and selection of viable targets for new medicines.



Constraints of Preclinical Models

Current preclinical models (e.g., animal models) of Alzheimer's disease are limited in the extent to which they can be extrapolated or translated to the human condition. Improved models are needed to facilitate preclinical testing of drug candidates and better predict their effects in humans.

Limitations in Early Diagnosis

Without validated, non-invasive biomarkers, it is difficult to identify disease presence, often resulting in diagnosis being delayed until symptoms become more pronounced. In the context of clinical trials, this makes it particularly challenging to identify eligible patients and enroll and retain them in clinical trials. It also makes it challenging to assess the effects of drug candidates. Ultimately, this leads to long and very expensive clinical trials.

Overcoming these challenges is crucial to the success of drug development in Alzheimer's. Given the complexity of the basic research and technologies that enable drug development, collaboration across multiple stakeholder groups — including the biopharmaceutical industry, government, academia, patient advocacy organizations, and disease foundations — is important to advancing the field as a whole. (See "Collaboration: Key to Innovating Medicines and Identifying Novel Biomarkers" on page 11.)

COLLABORATION

Key to Progress Against Alzheimer's

Tackling a disease as complex as Alzheimer's will require the combined efforts and brainpower of researchers across institutions. Biopharmaceutical companies are collaborating with patient advocacy groups, government agencies, and others in the hopes of soon delivering therapeutic advancements to Alzheimer's patients. Below are three examples of innovative partnerships that are bringing together the brightest minds to overcome one of society's great challenges.

UsAgainstAlzheimer's AD-PACE Program

In May 2018, UsAgainstAlzheimer's launched a multi-phased collaborative with pharmaceutical companies, advocacy organizations, academic institutions, and care services organizations to identify and prioritize the needs and preferences of those living with and affected by Alzheimer's disease. The partnership, Alzheimer's Disease Patient And Caregiver Engagement (AD-PACE), brings together Alzheimer's patients and caregivers to ensure that their perspectives are integrated into clinical trial design, drug development, regulatory reviews, payer value models, coverage and payment determinations, and research on care and services. According to Ian Kremer, Executive Director of the Leaders Engaged in Alzheimer's Disease (LEAD) Coalition, the collaboration is grounded in the belief that "every stage of Alzheimer's drug development should be centrally-informed by the preferences and priorities of people living with the disease."

Accelerating Medicines Partnership – Alzheimer's Disease

The Accelerating Medicines Partnership for Alzheimer's Disease (AMP-AD) is a collaboration among government agencies, including the National Institutes of Health (NIH) and FDA, 12 biopharmaceutical and life sciences companies, and several nonprofit organizations.[46]

Alzheimer's disease is one of the three target disease areas for the partnership. AMP-AD focuses on advancing the discovery of novel, clinically relevant therapeutic targets and the development of biomarkers to help validate existing therapeutic agents.

AMP-AD's approach is two pronged. First, researchers are exploring the utility of tau imaging and novel biomarkers in indicating response to treatment. AMP is providing supplemental PET imaging and fluid biomarkers for three large, ongoing clinical trials, allowing the researchers to gain additional information on the ability of these techniques to track the impact of treatments.[47] The second prong is an effort to accelerate the discovery and validation of disease drug targets by creating a large network of data, pooling molecular information from more than 2,000 patients. These data are available to researchers.

AMP's ultimate goal is to shorten the time between the discovery of a target and the development of an effective new medicine.[48]

Alzheimer's Disease Neuroimaging Initiative

The Alzheimer's Disease Neuroimaging Initiative (ADNI) launched in 2004 as a collaboration initiative between the NIH and other federal agencies, nonprofit organizations, and biopharmaceutical companies to develop ways to detect Alzheimer's disease at its earliest stages and track its progression through biomarkers. This work is designed to support and speed up the development of new therapies by making it possible to measure their effects more readily and select patients in early stages of the disease that may benefit the most.

Data collected from ADNI are made available at no cost to researchers to use as they design Alzheimer's disease clinical trials and related research efforts.[49]

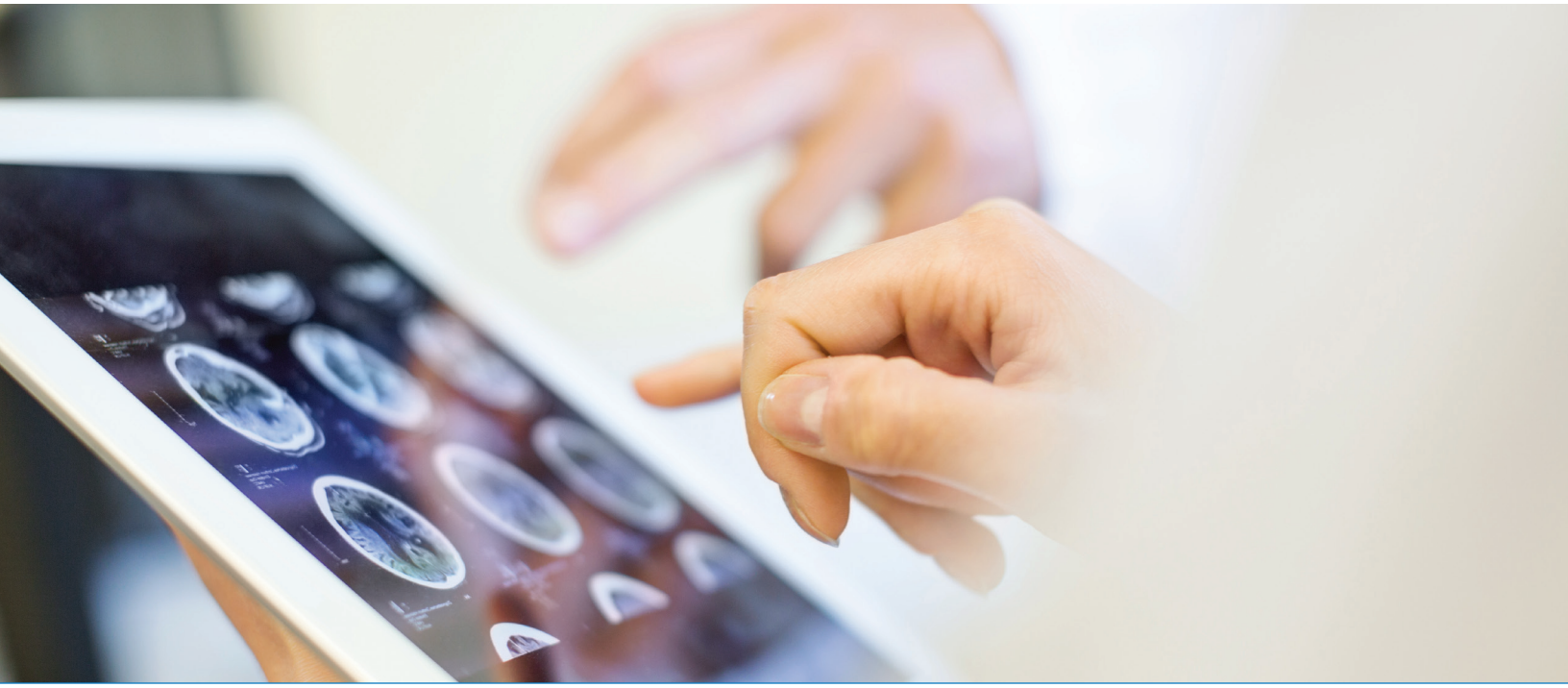
The Nature of Alzheimer's Research: Setbacks and Stepping Stones

Despite numerous studies and significant investment by biopharmaceutical companies and others, setbacks continue to outnumber successes in Alzheimer's drug development.

In general, few candidate medicines reach patients — only 12 percent of all medicines that enter clinical trials will eventually be approved by the FDA.[50] While by some measures trials that do not produce viable therapies may be considered "failures," these setbacks can be tremendously valuable, as they provide crucial insights that help shape future research efforts. As the data from a negative outcome are analyzed, the key findings are applied in the design of new studies and approaches, until ultimately a successful outcome or proof-of-concept for a new therapy is achieved.

Although every discontinued or suspended drug development project is extremely disappointing, progress is the result of successes and setbacks. Medical research is often iterative, and breakthroughs rarely happen overnight.

> "A failed experiment is the only one that does not give you more information. These aren't failures because we are still learning so much about the brain. They are putting us on the road to pursue progress together."
>
> **Phyllis Ferrell, Vice President of the Global Alzheimer's Disease Team at Eli Lilly and Company[51]**



> “Though deeply disappointing for both patients and researchers, these setbacks offer important insights that inform and redirect future research efforts. Patients with neurological conditions have a tremendous need for new treatments. Our industry is committed to tackling these devastating and complex conditions.”
>
> **Darryle Schoepp, Vice President of Neuroscience Discovery Pre-Clinical Early Development at Merck**[52]

Researchers Perspectives on Setbacks

It is difficult to quantify the ways that research setbacks contribute to eventual successes in developing a new treatment, but researchers attest to the insights gained through these efforts. For example:

In 2016, Eli Lilly and Company halted the Phase 3 clinical trial for solanezumab, an investigational drug that researchers hoped would slow the progression of memory problems associated with the buildup of amyloid in the brain.[53] Reflecting on this trial, **Frank Longo, Chair of Neurology and Co-Leader of the Stanford Neuroscience Health Center**, said,

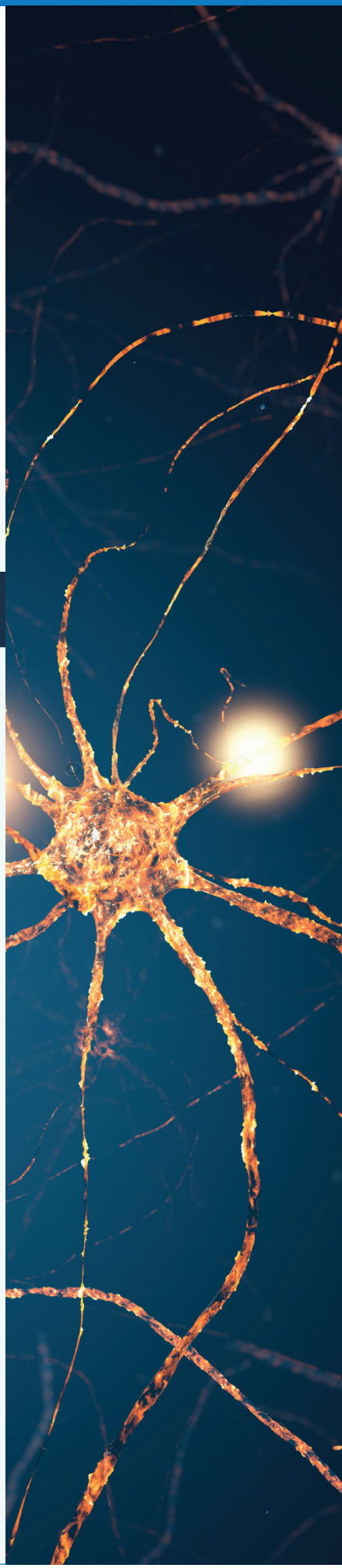
> “Even if it’s unfortunate news, each trial is tending to teach us a lot and the progress is being made faster because of that and it’s giving many in the field confidence that we will have a drug that does work at some point.”[54]

Referring to the same study, **James Hendrix, Director of Global Science Initiatives at the Alzheimer’s Association**, said,

> “As long as we continue to learn and advance our knowledge, we are getting closer. The problem is that we don’t know where the top of the mountain is, we don’t know if we have three more steps or three more miles or three hundred more miles to go, but we know we’re making progress, we’re learning more and more about the disease.”[55]

Three months later, Merck announced that it had halted its clinical trials of verubecestat.[56] **Bryce Vissel, Director of the Centre of Neuroscience and Regenerative Medicine at University of Technology Sydney**, acknowledged the importance of the trial, stating,

> “We must continue to pursue this disease. There’s good reason to have hope and optimism that with the pursuit of excellent science and some rethinking about [Alzheimer’s], a treatment will become available for this devastating disease in our lifetimes.”[57]



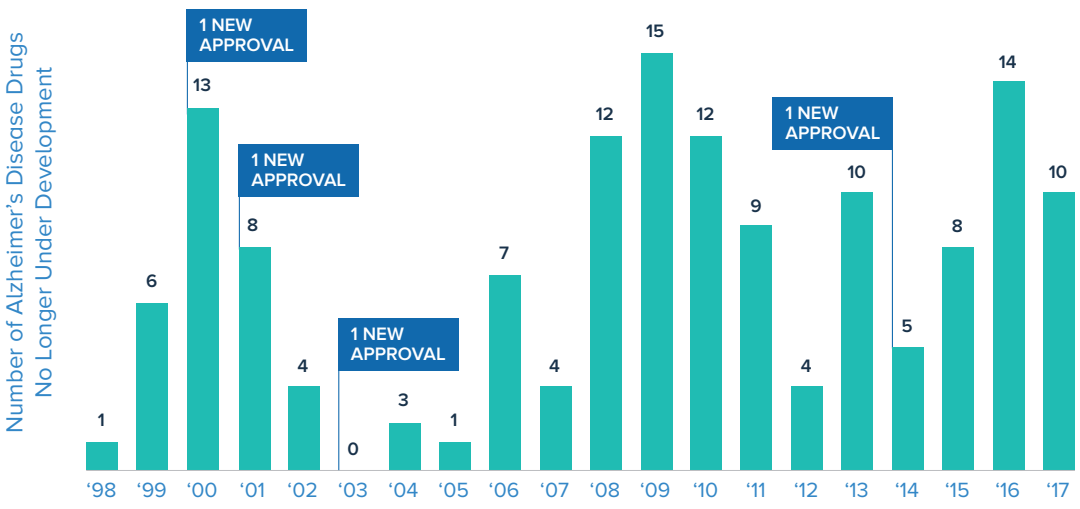
Quantifying Setbacks

In recent years, we have seen a steady stream of drug candidates in development, accompanied by a long series of unsuccessful outcomes. The number of investigational drugs studied for the treatment of Alzheimer's disease failing to reach patients each year offers a metric of both the scientific complexities and other difficulties associated with the research and development process. They also demonstrate the commitment of research-based biopharmaceutical companies to discovering new treatments for the disease.

Between 1998 and 2017, **146 investigational medicines** in clinical development have been halted and have not received regulatory approval, according to an examination of data from the Adis R&D Insight database.[58] An analysis of the phase of development of unsuccessful investigational drugs (see chart on page 15) showed that the largest portion (40%) were in early clinical trials including Phases 0, 1, or 1/2 but nearly as many were in Phase 2 or 2/3 (39%) and a substantial portion (18%) were in Phase 3 or regulatory review. A substantial number of candidates made it into the more costly later stages of clinical development. The "inactive" category includes investigational studies that are labeled by the database curators as "discontinued" (definitively halted), "suspended" (halted for the foreseeable future), or have "no development reported" (no evidence of continued research in the past 18-24 months. A detailed note on methodology and definitions is included at the end of this report. It is important to note that this analysis does not include investigational drugs that did not advance beyond preclinical development (i.e., never reached studies in humans).[59]

Since 1998, **four new medicines** for Alzheimer's have been approved, resulting in an approximately **37 to 1 ratio** of "failures" to approvals (one other medicine that is currently in use was approved before this timeframe, for a total of five approved medicines).[60] This ratio represents about a 2.7 percent success rate to date, illustrating the complexity and challenges of the Alzheimer's drug discovery and development process.

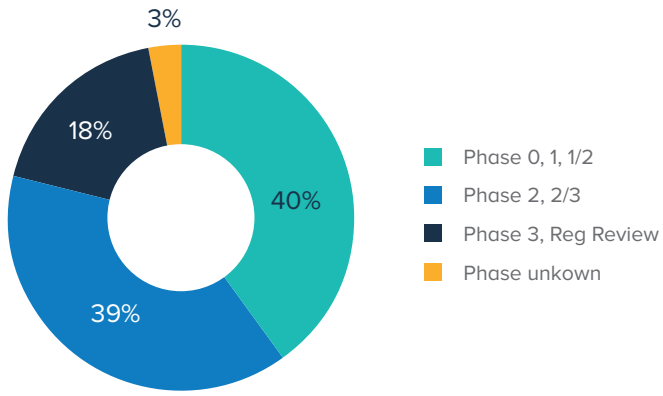
Unsuccessful Investigational Drugs for Alzheimer's Disease (1998-2017)



146 Total Unsuccessful Drugs | **4** Total Approved Medicines

Source: PhRMA analysis of Adis R&D Insight Database, 25 January 2018

Unsuccessful Investigational Alzheimer's Drugs by Phase (1998-2017)

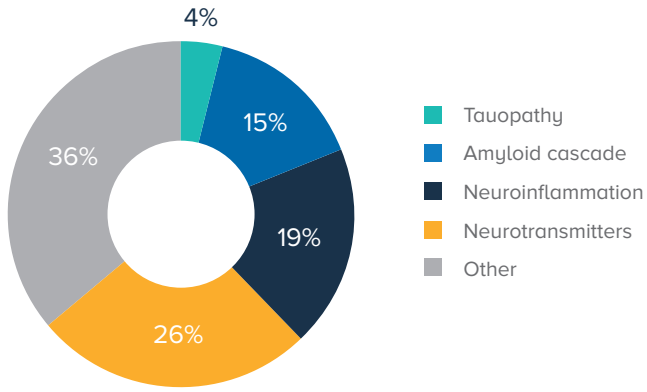


Source: PhRMA analysis of Adis R&D Insight Database, 25 January 2018

Setbacks are an inevitable part of the drug research and development process. Each of these unsuccessful efforts provides critical insights that help shape the future direction of Alzheimer's research. The large number of investigational drugs that have fallen short year after year demonstrates both the difficulty of this endeavor as well as researchers' unwavering commitment to developing improved diagnostics and new treatments for this devastating disease.

Other research has examined the scientific approaches taken by unsuccessful Alzheimer's candidates and found that the majority of R&D investment in Alzheimer's has focused on the amyloid cascade, tau aggregation, neuroinflammation, and neurotransmission.[61] As of March 2016, almost half of all discontinued research related to investigational drugs in this space attempted to mitigate neuroinflammation and address neurotransmitter signaling in the brain.[62] Approximately 19 percent of candidates targeted the amyloid cascade pathway and tau protein aggregation.[63] (See chart below.)

Mechanistic Classes of Discontinued Investigational Drugs for Alzheimer's Disease



Source: Nature Reviews Drug Discovery, "Trial watch: Tracing investment in drug development for Alzheimer disease," December 2017, https://www.nature.com/articles/nrd.2017.169

On the Front Lines

with Matthew Kennedy, Director Early Discovery Neuroscience at Merck & Co. Inc.

Q **How has the progression of research on Alzheimer's treatments changed over your career as a researcher?**

A When I first started working on this problem as a drug discovery scientist about 20 years ago, we had a wealth of new information about what we thought were the likely molecular mechanisms of Alzheimer's disease. For example, we had incredibly powerful human genetic data that told us that the production of these Abeta peptides that form the plaques had to be an essential part of the disease. As a result, when I first joined Merck, I was lucky to be part of a very large team that focused on developing a small-molecule inhibitor of an enzyme we call BACE1 that is responsible for making that Abeta peptide. So, we had a very clear focus of what we were trying to achieve back then. But I think in retrospect what we were missing then — and what the field has filled in dramatically over the ensuing years — is a lot more information about what's actually happening in the brains of living humans who either have the disease or who are at high risk for the symptoms of disease through the discovery and study of biomarkers of Alzheimer's pathology.

Q **What are some of the biggest challenges with Alzheimer's research today and how are researchers tackling these challenges?**

A I think one of the biggest challenges we have in our research today is that we don't have ways of authentically modeling Alzheimer's disease in animals. We can use animal models to give us very specific information about the molecular mechanism and pharmacology of drugs that we are developing, but our big challenge is that mice don't get Alzheimer's disease. So, while we can engineer them to show one particular part of the disease process and study that carefully, that doesn't allow us to predict whether the activity we see in animals will provide benefit to people. So right now, we are focused on trying to build more authentic animal models of the disease, which can provide a snapshot of the diverse changes in the Alzheimer's brain. For example, we are studying how the brain's immune system reacts to Alzheimer's pathology so that we can study experimental immune-modifying therapies in a controlled way. Another way is to use stems cells from patients to produce human neurons and mini-brains in culture that can more accurately mimic human disease.

Q **How would earlier diagnosis impact how we research and potentially bring a new treatment to Alzheimer's patients?**

A Earlier intervention — well before symptoms set in — will likely be our best chance of truly modifying the course and prevalence of Alzheimer's disease. Achieving this will require having biomarkers that accurately identify if a person has the earliest signs of Alzheimer's pathology in their brain. Genetic, imaging and cerebrospinal fluid biomarkers are effective at defining risk and revealing amyloid plaques and tau tangles, but to reach the wider population of people at risk for this disease, we will need blood-based biomarkers. Blood tests would be more widely accessible and recent progress suggests that this is possible. Experimental treatments will need to safely slow or stop progression of these Alzheimer's pathology biomarkers, but that will not be enough. Since the earliest stage patients will have no obvious symptoms, we need much more sensitive tests of brain function. I am most excited about emerging digital technologies that may work through wearable sensors or through a mobile phone to provide a real-world view into how a person is navigating their daily life.

Continuing to Innovate

Promising Pipeline

Despite challenges, a robust pipeline of medicines in development represents our greatest hope in addressing the societal and economic burden of Alzheimer's disease.

Biopharmaceutical companies are currently researching **92 new potential medicines**.[64] An analysis by UsAgainstAlzheimer's of medicines in development found that of those in Phases 2 and 3, approximately 75 percent have the potential to be disease-modifying treatments.[65] These drug candidates could stop or slow down disease progression by targeting one or more of the changes in the brain associated with the disease. The majority of drugs in the pipeline target beta-amyloid plaques, tau protein tangles, and a receptor that decreases a neurotransmitter necessary for the brain to think and function normally.[66]

Supporting Progress

Despite this promising pipeline, the substantial complexity of Alzheimer's disease indicates that we must be prepared for many more setbacks before researchers discover how to prevent, halt, or cure Alzheimer's. Together with stakeholders across the research ecosystem, biopharmaceutical researchers and the companies they work for are committed to overcoming setbacks and applying the insights gained to pursue new medical advances.

The findings in this report illustrate why it is important to support a broad and vibrant research enterprise to foster this progress. Thoughtful public policies are needed that encourage innovators to continue taking the risks, making the substantial research investments required, and building upon setbacks to achieve eventual success against serious diseases and conditions like Alzheimer's disease.

We applaud the FDA's commitment to continue to modernize its drug regulatory programs and its efforts to keep pace with the latest scientific developments. For example, in 2018, FDA issued guidance to inform research efforts into interventions that stop Alzheimer's disease before it causes clinical problems. This guidance provides innovators with important information on "approaches to studying very early disease before the onset of dementia, including strategies for trials incorporating patients with Alzheimer's who haven't experienced any visual impairment (in the form of cognitive or functional deficits), but who may be identified through the use of sensitive cognitive screening, imaging tests, or biomarkers."[67]

As the aging population expands, so does the need to address and conquer Alzheimer's disease. Without future progress, the cost and resource burden of Alzheimer's will continue to grow, and countless individuals and families will be impacted. However, with continued commitment from biopharmaceutical companies and other research partners, we can overcome significant challenges, change the course of this disease and, ultimately, prevent Alzheimer's patients from becoming Alzheimer's patients in the first place.

> "Despite recent failures, we have learned a lot and have much reason to be optimistic. This is particularly true when it comes to early intervention approaches, where the latest science is telling us we have the greatest opportunity to impact disease progression – an area of somewhat uncharted territory in the history of Alzheimer's disease drug discovery."
>
> **John Dunlop, Vice President of Neuroscience Research at Amgen[68]**

A note on methodology:

Data are drawn from the Adis R&D Insight database which compiles publicly available information on potential medicines in development. Candidate drugs included were categorized in the database as "suspended," "discontinued" or "no development reported" for the indication "Alzheimer's disease." Only projects in clinical development, phase unknown, or Food and Drug Administration review were included. In cases where more than one delivery mechanism was tested, or where the history included more than one category from our list (e.g., "no development reported" in 2006 and "suspended" in 2007), the latest date included was counted.

ADIS' DEFINITIONS:

Discontinued	"The company has chosen to stop development."
No development reported	"If there has been no activity associated with a drug (no commercial information released, no recently published studies) for 18 months to 2 years, the term 'no development reported' is assigned. The time frame depends on the last phase of the drug. This is the term used until a drug is confirmed as discontinued, withdrawn or suspended, or activity is resumed."
Suspended	"This term is used when a company has suspended development of a drug, often in order to focus on the development of some other drug. Development has not been discontinued."

According to Adis R&D Insight database editors regarding "inactive" projects, they report that although exact percentages are not available, only a very small proportion of projects categorized as "no development reported" are reactivated, and the majority go on to be "discontinued" after more time has elapsed. "No development reported" status is used when development goes silent, and the editors see that no activity appears to be happening. They use the term "suspended" when a company states that it is suspending development for any reason. It is difficult to determine what percentage of these programs are reactivated because it depends whether another company picks up a license to develop it or whether the company itself will reactivate development at another stage. Generally, when a company suspends development a very small percentage of drug programs are reactivated by the same company. A small percentage of suspended projects are out-licensed, at which point the chances of reactivation become much higher. There is a very small percentage of discontinued programs that are reactivated.

The analysis goes back to 1998, as the Adis data are less comprehensive before this time. Data are current as of January 25, 2018, but do not include partial year data from 2018.

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