Researching Alzheimer’s Medicines: Setbacks and Stepping Stones
Summer 2015
Foreword

Alzheimer’s disease is the only one of the leading causes of death in America without a way to cure, prevent or even slow its progression. Thanks to hard work on many fronts, the effort to change this unacceptable fact is at last becoming a true national priority.

There is increasing bipartisan support for significantly increasing the appropriated amounts for Alzheimer’s research within the National Institutes of Health budget. NIH investment plays an important role in advancing research on Alzheimer’s. Additional resources will enable NIH to do so more effectively.

Ultimately, however, we all know new treatments will be developed and delivered through the pharmaceutical industry. As this important report documents, pharmaceutical companies have committed substantial resources and expertise toward changing the trajectory of Alzheimer’s through better treatments, and we need this to continue. While these investments have not yet yielded the breakthroughs we need, they have brought us much closer to that day.

That is why both the Alzheimer’s Association and its sister organization, the Alzheimer’s Impact Movement, place such a high emphasis on collaborating with industry partners, just as we do with government and academia. When industry finally delivers the treatments we need, our constituents – millions of Americans – are the ones who stand most to win.

We are on the right path toward a much better future. But we must continue to accelerate our efforts. With Alzheimer’s immense and steadily growing impact, we have no time to lose.

Robert Egge
Executive Director
Alzheimer’s Impact Movement
Executive Summary

Alzheimer’s disease is a devastating disease that causes individuals to lose their memories, independence, relationships, and, ultimately, their lives. Family and caregivers face many challenges as they care for a loved one who is gradually slipping away. From a societal perspective, Alzheimer’s has not only a human but also a financial cost — particularly on the health care system — which will only increase in the coming years as the number of Alzheimer’s patients grows.

Innovative new medicines are needed to treat, slow, and prevent Alzheimer’s disease. Biopharmaceutical research companies are studying many potential new treatments. However, the path from basic research to new drug treatments is extremely long and complex with many setbacks along the way, particularly in the case of Alzheimer’s disease.

A new analysis finds that between 1998 and 2014, there were 123 unsuccessful attempts to develop drugs to treat Alzheimer’s – or as some call them “failures.” In that timeframe, four new medicines were approved to treat the symptoms of Alzheimer’s disease; for every research project that succeeded, about 30 failed to yield a new medicine.

Although these setbacks are deeply disappointing, they often contribute to eventual success by helping guide and redirect the work of scientists investigating potential new drugs. With so much to learn and understand about the brain and neurological diseases like Alzheimer’s, researchers take the findings from the unsuccessful projects and use that information to continue searching for new medicines.

While these setbacks are valuable to researchers, they also are very costly and illustrate the long and uncertain process of developing medicines for diseases as complex as Alzheimer’s. They serve as a reminder that to make progress, we need 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 finding treatments that realize the promise of our expanding scientific knowledge to halt or prevent disease. Researchers are currently working on 59 medicines in development for Alzheimer’s and other dementias. They give patients – and future patients – hope for a future free of Alzheimer’s disease.
This is an exciting time in Alzheimer’s research. After many challenging years, we are gaining a better understanding of how the disease progresses, leading to the development of promising investigational therapies and important new approaches to test them. These advances are providing hope that soon we may be able to alter the course of this disease and improve the lives of millions of patients and those who care for them.

Alfred Sandrock, M.D., Ph.D.,
Group Senior Vice President and Chief Medical Officer, Biogen²

Introduction

The discovery and development of new medicines is essential in addressing the unmet needs of our most challenging and devastating diseases. This is particularly true for Alzheimer’s disease, where the development of innovative new medicines to prevent or slow the disease’s onset and progression will have a profound impact on the lives of millions of people.

Such impact is usually recognized once a new medicine becomes available to patients. What is often less recognized (or forgotten) is the complexity that lies beneath the research and development which made that innovative medicine possible. The process is not a straight line from basic research to new treatment. Rather, the extraordinary complexity of developing a medicine that is safe and effective means many setbacks typically occur along the way.

This report highlights the burden of Alzheimer’s disease, the challenges of researching it, and the setbacks and advances we have seen in our efforts to overcome this daunting illness.

We are entering an era of medical innovation that offers a real chance to find therapies for some of the most challenging diseases, from Alzheimer’s, to ALS, to many of the cancers that now have few or no treatments. Success will require not only superior science but also sound public policy.

Ian Read
Chairman of the Board and CEO, Pfizer³
The Impact on Individuals and Families

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

Individual patients are not the only ones affected by Alzheimer’s. Family and other caregivers are another casualty of the disease. They carry an enormous burden – emotionally, physically, and financially.

According to the Alzheimer’s Association, about 5.3 million people are currently affected by the disease. It is the sixth leading cause of death in the United States today, although recent studies suggest that Alzheimer’s deaths are underreported.

“In many ways, my father always seemed larger than life. To see this disease take away his brain was devastating.”

KEN FRAZIER, J.D.
CHAIRMAN AND CEO, MERCK

“In contrast to caregivers of patients with other terminal illnesses, who may experience a degree of anticipatory grief, caregivers of those who have Alzheimer’s disease endure the anguish of caring for a loved one who, in many respects, is already gone.”

HOLLY G. PRIGERSON, PH.D.
PROFESSOR OF SOCIOLOGY IN MEDICINE, WEILL CORNELL MEDICAL COLLEGE
The Economic Cost

Alzheimer’s disease accounts for $226 billion each year in direct medical costs, due in part to the cost of nursing home care. The indirect costs are at least as high, and difficult to fully estimate. The number of individuals caring for Alzheimer’s patients – often family and friends – reached 15.7 million in 2014, providing nearly 18 billion hours of unpaid care valued at more than $217 billion.\(^8\)

The scope and economic burden of Alzheimer’s is only expected to grow in the coming years. The number of people with Alzheimer’s is projected to grow every year to reach a total of 13.5 million patients in 2050, up from 5.3 million today.\(^9,10\) On this trajectory, the direct cost of Alzheimer’s disease in adults 65 and older could balloon to $1.1 trillion in 2050 (in today’s dollars) with a total of $20.8 trillion in medical costs between 2015 and 2050, according to the Alzheimer’s Association.\(^11\)

New disease-modifying treatments could change these projections. According to the same report, a new treatment approved by 2025 that delays the onset of Alzheimer’s by five years would reduce the number of people with the disease by approximately 40% and reduce the cost for care of Alzheimer’s patients by $367 billion a year by 2050. (See chart below.)\(^12\)

Researchers across the country in biopharmaceutical companies, academia, and government are determined to develop such treatments.

![Projected Impact of a Medicine that Delays Alzheimer's Disease Onset by 5 Years, 2015-2050](chart.png)

Understanding Alzheimer’s

While the cause of Alzheimer’s remains unknown, our understanding of the disease, including potential ways to attack or prevent it, has advanced in recent years.

Molecular and Genetic Underpinnings

At the molecular level, scientists are beginning to unravel the processes that occur as Alzheimer’s disease progresses, but much of the biological causes and underpinnings of the disease remain a mystery. Research has demonstrated several features in the brain that may be indicators of, or contribute to, the disease. For example, that abnormal fragments of a protein called beta-amyloid accumulate to form “plaques” in the brain of individuals with Alzheimer’s, particularly in regions that support memory.13,14

Another hallmark of Alzheimer’s is the formation of “neurofibrillary tangles” inside neurons (brain cells). The tangles are twisted fibers consisting primarily of a protein called tau. Tau is a component of microtubules, which help transport nutrients and other important elements in cells and provide cell structure.15,16

Researchers have improved their understanding of the role of these plaques and tangles in this process but still have more to learn.17,18 It remains unclear whether these molecular changes are causes or symptoms of the disease.19 Ultimately, neurons lose the ability to communicate and they die, which results in atrophy of the brain regions affected.

Researchers are also working to understand the role of other pathological features associated with Alzheimer’s such as inflammation and insulin resistance.20

Alzheimer’s disease is believed to be caused by a combination of genetic, environmental, and lifestyle factors. There have been some advances in understanding the genetic component of the disease, although progress has been limited. Less than 5% of cases are familial, which means that some members of the family carry a gene that guarantees they will develop Alzheimer’s, usually with an early onset.21,22 These cases have been linked to mutations in the amyloid precursor protein and presenilin encoding genes.23 Variations in certain genes, such as the apolipoprotein E genes, may also play a role as risk factors, whereas research has also suggested that certain genes may play a protective role against developing Alzheimer’s.24,25,26
Earlier Diagnosis

It has been well established that Alzheimer’s disease begins years or decades before symptoms become noticeable. Many researchers believe that diagnosis and treatment in these early stages will be paramount to stopping the disease before it does irrevocable damage.

Today, the diagnosis of Alzheimer’s disease is based primarily on patient history and clinical evaluation, including neurological and neuropsychological assessment, and often it is made by excluding other conditions.

However, researchers from biopharmaceutical companies, government, academia, and others are actively collaborating to improve the diagnosis of Alzheimer’s disease. Their goal is to both increase accuracy and improve earlier diagnosis using imaging and non-imaging biomarkers – a molecule or other biological attribute that can be measured to indicate the presence of disease. (See “Collaboration: Key to Advancing Alzheimer’s Research” on page 10.)

Some imaging techniques help rule out the presence of other conditions and some specifically reveal evidence of Alzheimer’s in the brain. In particular, positron emission tomography (PET), in combination with various radiochemicals, can be used to visualize both amyloid plaques and neurofibrillary tangles in the brain. Another imaging technique, called single-photon emission computed tomography (SPECT) appears to be helpful in differentiating the disease from other brain conditions. Recent clinical trials have used PET and magnetic resonance imaging (MRI) as a way to confirm the diagnosis of Alzheimer’s as well as to identify potential disease-modifying effects in research participants.

Non-imaging biomarkers, including molecules measured in the blood, urine, cerebrospinal fluid, or other parts of the body may also prove to be useful tools in the diagnosis and monitoring of Alzheimer’s. For example, researchers are focusing on biomarkers that indicate the level of beta-amyloid in the brain, and those indicating that neurons are either damaged or deteriorating.

Researchers believe that biomarkers will eventually be critical for identifying individuals with early stage Alzheimer’s and monitoring the effects of treatment. As our ability to reliably diagnose the disease grows so does our ability to develop effective treatments.

“[Alzheimer’s disease] research has developed to the point where scientists are looking beyond treating symptoms to addressing the underlying disease process.”

National Institute on Aging
Challenges of Developing Alzheimer’s Medicines

Despite increasing understanding of Alzheimer’s disease, developing a medicine to prevent, delay, slow, or cure it is exceptionally difficult. Years of research have yielded only a handful of medicines that provide some symptomatic relief in some cases but we do not yet have an approved disease-modifying medicine. (See “Today’s Treatments” on page 11.)

There are many reasons Alzheimer’s research is so challenging. For example:

• As detailed above, progress has been made, but scientists still do not understand the underlying causes and mechanisms of the disease. In fact, it is unknown whether many of the defining molecular characteristics of the disease are causes, effects, or signs of progression. This scientific knowledge gap makes the identification and selection of viable targets for new medicines difficult.

• 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. Better models are needed to facilitate preclinical testing of drug candidates and better predict the effects of the drug in humans.

• The absence of validated, non-invasive biomarkers to identify disease presence and progression means diagnosis is delayed until an individual becomes symptomatic. This makes it particularly challenging to evaluate, enroll, retain, and follow up with patients in clinical studies. It also makes it challenging to assess the effects of the drug candidate. 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, collaborations among multiple stakeholders – including the biopharmaceutical industry, government, academia, patient associations, and disease foundations – are important to advancing the field as a whole. (See “Collaboration: Key to Advancing Alzheimer’s Research” on page 10.)

Researchers believe that no single medicine will be able to defeat Alzheimer’s; rather, several medicines will probably be needed to combat the disease. As a result, researchers need not one, but an array of options to prevent or treat Alzheimer’s disease.
The enormity of the complexities and unknowns regarding Alzheimer’s disease means that no single company, institute, or organization can tackle the disease alone. Many collaborations exist in the world of Alzheimer’s research; here are just two examples:

**Alzheimer’s Disease Neuroimaging Initiative (ADNI)**
Since 2004, the Alzheimer’s Disease Neuroimaging Initiative (ADNI) has brought together the National Institutes of Health (NIH), other federal agencies, non-profit organizations, and innovative biopharmaceutical companies with the central goal of finding ways to detect Alzheimer’s disease at its earliest stages and track its progression through biomarkers. ADNI researchers use tools such as MRI and PET scans, and cognitive testing, in conjunction with blood and cerebrospinal fluid samples, to measure biomarkers and look at changes in the brains of participants with normal cognitive function, mild impairments, and Alzheimer’s disease.

This work is designed to support and speed 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.

**Accelerating Medicines Partnership – Alzheimer’s Disease (AMP-AD)**
The Accelerating Medicines Partnership (AMP) is a collaboration among the NIH, 10 biopharmaceutical companies, the U.S. Food and Drug Administration (FDA), and several non-profit organizations with the goal of sharing knowledge and other resources to speed the identification and validation of promising biological targets to foster development of treatments for chronic diseases.

Alzheimer’s disease is one of the three disease areas of focus for the partnership, and the approach is two pronged. First, a biomarkers project is exploring the utility of tau imaging and novel fluid biomarkers in indicating response to treatment. AMP is providing supplemental PET imaging and novel fluid biomarkers for three large, ongoing clinical trials, allowing the researchers to gain additional information on the ability of these biomarkers to track the impact of treatments.

The second prong is an effort to discover and validate 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 and is housed in the AMP-AD Knowledge Portal. AMP’s ultimate goal is to shorten the time between the discovery of a target and the development of an effective new medicine.
Today’s Treatments

Although ways to prevent, treat, or cure Alzheimer’s disease are clearly still needed, we have made some progress in controlling its symptoms. Before the 1990s, there were no medicines for Alzheimer’s. Currently, there are five FDA-approved medicines to help manage Alzheimer’s symptoms, including memory loss, thinking, and reasoning problems. Unfortunately, these medical treatments do not work for every patient, they cannot cure the disease or stop its progression, and when they work, their beneficial effects often decrease over time.\textsuperscript{41,42,43}

However, many experts urge early treatment with these existing medicines when they can be most effective in controlling patients’ symptoms.

\textquoteright Most medications for Alzheimer’s disease are most effective when taken early in the disease, although available treatments are useful only for slowing the progression of symptoms—not modifying the disease outcome…. Many studies have shown the benefits of the treatments on biologic (brain scans), psychological (cognitive testing and behavioral testing) and social (activities of daily living or ADL) measurements.\textquoteright

\textit{Alzheimer’s Foundation of America}\textsuperscript{44}
The Nature of Alzheimer’s Research: Setbacks and Stepping Stones

Setbacks have greatly outnumbered successes in Alzheimer’s drug development. This is not only due to the complexity and challenges of researching this particular disease, but it also simply reflects the nature of drug discovery and development. Across all diseases, only 12% of medicines that enter clinical trials will eventually be approved by the U.S. Food and Drug Administration. In biopharmaceutical research, setbacks are common, but each one helps advance our knowledge and guides next steps and new solutions.

To some, candidate medicines that never reach patients can only be considered “failures,” but others recognize that they provide new information that biopharmaceutical researchers can use to build on going forward. As the data from a negative outcome are analyzed, the key findings are applied in the design of new experiments 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.
Researchers’ Perspectives on Setbacks

It is difficult to quantify the ways that each research setback contributes to eventual successes in developing a new treatment, but many researchers attest to the importance of this information. For example:

• In the face of the disappointing clinical results of an investigational drug which targeted beta amyloid plaques in 2012\textsuperscript{46}, the global head of neuroscience drug development at Janssen Research & Development, LLC, Husseini Manji, M.D., said, “When we got into this, we realized it was one of the most challenging things we could take on...You hope your first approach works, but we are certainly going to learn a lot from this data.”\textsuperscript{47}

The lead researcher of the bapineuzumab research, Stephen Salloway, a professor at the Warren Alpert Medical School at Brown University said, “We always want to get a home run, especially for a bad disease like Alzheimer’s disease, but you have to learn as much as you can and there are a lot of things we got out of these studies that we are incorporating into new trials.”\textsuperscript{48}

• In 2013, Baxter International announced that the Phase III trial of its immunoglobulin (IG) therapy did not reduce cognitive decline and preserve function in patients with mild to moderate Alzheimer’s disease as hypothesized. Norman Relkin, M.D., the study leader and neurologist from Weill Cornell Medical College acknowledged the importance of the trial efforts, saying, “Analysis of the full study results is still ongoing. I am optimistic that the knowledge we gain from this study will advance efforts to develop effective treatments in Alzheimer’s disease.”\textsuperscript{49}

"Every study provides an opportunity to learn more about the science and how to improve the next study. Each shot on goal, whether a hit or a miss, positive or negative, brings us closer toward an effective treatment."

\textbf{Maria C. Carrillo, Ph.D.}
\textbf{Chief Science Officer, Alzheimer’s Association}\textsuperscript{50}
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 difficulty of the endeavor and the commitment of the biopharmaceutical industry to finding better treatments for the disease.

Between 1998 and 2014, 123 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. The “inactive” category includes investigational studies that are labeled by the database curators as “discontinued” (definitely halted), “suspended” (halted for the foreseeable future), or have “no development reported” (no evidence of continued research in the past 18-24 months). Adis database editors report that the chance of reactivation of “inactive” projects is very small. (See detailed note on methodology and definitions at the end of this report.) It is important to note that this analysis does not include drugs that did not advance beyond preclinical development (i.e., never reached studies in humans).

“"There are a lot of people pursuing a number of different approaches and I’m really hopeful that within the next few years some of them will pan out and provide the answers to what is a terrible problem.”

David Michelson, M.D.
Vice President, Neuroscience and Ophthalmology Clinical Research, Merck Research Laboratories

“"On one side, you have massive social problems that are still not solved, like Alzheimer’s, mental health disorders, oncology, and on the other side, you have science moving at a breathtaking pace.”

Joaquin Duato
Worldwide Chairman, Pharmaceuticals, Johnson & Johnson
Since 1998, **four new medicines** for Alzheimer’s have been approved, resulting in a **30 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). It should not be concluded that these numbers imply that every 30 setbacks will yield one new approval, but it provides an indication of recent research outcomes.

Each of these unsuccessful efforts provides much-needed data that allow researchers to draw conclusions that contribute to shaping the future direction of Alzheimer’s research. For example, one project may show some small benefit – although not enough to warrant further study or regulatory approval – leading researchers to go back to the drawing board to screen for a compound that may have similar, but more pronounced effects. In other cases, a candidate medicine may have no beneficial effect at all, so researchers can conclude such an approach should be abandoned. Regardless of the exact circumstances, all unsuccessful projects are opportunities to learn more about the disease.
Continuing to Innovate

Promising Pipeline

There is reason for optimism in the coming years as our grasp of the underlying causes and processes of Alzheimer’s disease continues to grow. About **60 new medicines** are currently in clinical trials or under FDA review for Alzheimer’s and other dementias by biopharmaceutical companies.54 The drugs in the pipeline take many different approaches to treating, stopping, reversing, or preventing the disease.

A recent study holds promise for the development of a new therapy that seeks to use the body’s own immune system to combat the disease in individuals with early stage Alzheimer’s.55 Several potential medicines known as beta-secratase inhibitors, which are designed to block production of amyloid beta, are in clinical studies and appear to affect the underlying disease processes; researchers are examining whether that translates into a clinical benefit.56 Studies are also examining the possibilities of targeting patients much earlier in disease stage and people with specific genetic variations.

Supporting Progress

Given the cumulative nature of medical research and the extreme complexity of Alzheimer’s disease, we must be prepared for many more setbacks before researchers discover how to prevent, control, or cure Alzheimer’s.

The findings in this report illustrate why it is important to support a broad and vibrant research enterprise to foster this progress. Thoughtful policies are needed that encourage innovators to continue taking risks and accepting setbacks to achieve eventual success against serious diseases and conditions like Alzheimer’s disease.

Biopharmaceutical Companies’ Commitment

Many biopharmaceutical company researchers – from scientists to lab technicians to statisticians and others – are committed to finding treatments that realize the promise of expanding scientific knowledge to halt or prevent disease. Many employees devote their entire careers to ending the burden of Alzheimer’s disease. Like many of us, they too may know someone who has suffered from Alzheimer’s, and they have seen the impact it has on individuals and families. In the face of often disappointing setbacks, researchers and others involved in R&D take the findings in stride and apply that new information to continue their quest.

As our population ages, Alzheimer’s is an important disease to address and conquer. Not only will the cost and resource burden balloon, but the disease will also engulf ever more individuals and their families. With continued determination, we can change the course of the disease and, ultimately, prevent Alzheimer’s patients from becoming Alzheimer’s patients in the first place.
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 June 17, 2015, but do not include partial year data from 2015.
References

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