Researching Alzheimer’s Medicines: Setbacks and Stepping Stones
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Executive Summary

Alzheimer’s disease is among the most devastating diseases anyone can face. Alzheimer’s patients lose their memories, independence, relationships and ultimately their lives. Family and caregivers are often pushed to their limits as they care for a loved one who is gradually slipping away. Fiscally, Alzheimer’s is a costly burden 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 complex with many setbacks along the way, particularly in the case of Alzheimer’s.

A new analysis presented in this report finds that since 1998, there have been 101 unsuccessful attempts to develop drugs to treat Alzheimer’s – or as some call them “failures.” In that time three new medicines have been approved to treat the symptoms of Alzheimer’s disease; for every research project that succeeded, 34 failed to yield a new medicine.

These setbacks often contribute to eventual success by helping guide and redirect researchers investigating potential new drugs. In the face of these deeply disappointing setbacks, researchers take the findings from the unsuccessful projects and use that new information to step forward and continue searching.

While these setbacks are valuable to researchers, they also are very costly. They serve as a reminder that in order to make progress we need a policy framework that supports the long and uncertain process of developing treatments as well as the successes by sustaining a robust research enterprise that 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. Dedicated researchers are currently working on nearly 100 medicines in development for Alzheimer’s and other dementias. They give patients and future patients hope for a future free of Alzheimer’s disease.
Introduction

The discovery and development of new medicines is essential to address 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 who face it today and in the future.

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 in the human body means many setbacks typically occur along the way. A new analysis presented in this report finds that since 1998 we have seen 101 unsuccessful drugs – or as some call them “failures” – for the treatment of Alzheimer’s. This means there have been 34 setbacks for every one approval in that period.

These setbacks often contribute to eventual success by helping guide and redirect researchers investigating potential new drugs. They also serve as a reminder that in order to make progress we need a policy framework that supports both the setbacks and the successes in developing treatments by sustaining a robust research enterprise that encourages innovators to take risks and accept the inevitable setbacks.

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

Alzheimer’s disease is among the most devastating diseases an individual can face. It gradually robs a person of everything they hold dear: their memories, all their relationships, their own 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 succumbed to this terrible disease and have seen the toll it takes.

Individual patients are not the only ones affected. Family and caregivers (often one and the same) are another casualty of the disease. They are often pushed to their limits both emotionally and financially.

According to the Alzheimer’s Association, it is the 6th leading cause of death in the U.S. today, with 5.4 million people currently affected. ¹

“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.
New England Journal of Medicine²
The Economic Cost

Alzheimer’s disease accounts for $200 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 often difficult to estimate comprehensively. The number of family, friends, and caregivers of Alzheimer’s patients reached 15.2 million in 2011, providing unpaid care valued at more than $200 billion.¹

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. On this trajectory, the direct cost of Alzheimer’s disease in adults over 65 could balloon to $1 trillion per year by 2050 (in today’s dollars) with a total of $20 trillion in medical costs in the next 40 years, according to the Alzheimer’s Association.²

New disease-modifying treatments could change these projections. According to the same report, a new treatment that delays the onset of disease by five years would reduce the number of people with the disease by nearly half and reduce the cost for care of Alzheimer’s patients by $447 billion a year by 2050. (See chart below.) A treatment that slows the progression of Alzheimer’s by five years would reduce the expected number of people in the severe stage of the disease by over 65% and save $197 billion a year by 2050.

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

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 unraveling the processes that occur as Alzheimer’s disease progresses. We know that abnormal fragments of a protein called beta-amyloid accumulate to form “plaques” in the brain of Alzheimer’s patients, particularly in regions that handle memory. 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 which is a component of the microtubules, a subcellular transport system for nutrients and other important elements.\(^5,6\)

Ultimately, neurons lose the ability to communicate and they die, which results in atrophy of the brain regions affected. Researchers have improved their understanding of the role of plaques and tangles in this process but still have more to learn.\(^7,8\) It remains unclear whether these molecular changes are causes or symptoms of the disease.\(^9\)

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

While Alzheimer’s is primarily a disease that is not genetically inherited, 0.1% of cases are familial, usually with an early onset. These cases have been linked to mutations in the amyloid precursor protein and presenilin encoding genes.\(^10\) Variations in certain genes, such as the apolipoprotein E genes, may also play a role as risk factors.\(^11\) Even so, our understanding of the genetics of Alzheimer’s, including its interplay with environmental risk factors, remains quite limited.

“We are at an exceptional moment scientifically for Alzheimer’s.... This is not about just celebrating where we’ve come from, but rolling up our sleeves to see where we can go.”

National Institutes of Health (NIH) Director
DR. FRANCIS COLLINS \(^15\)
Earlier Diagnosis:

It has been well established that Alzheimer’s disease begins years or decades before symptoms become noticeable. Unfortunately, definitive diagnosis of the disease is currently impossible until after a patient dies, as it requires direct microscopic examination of brain tissue. 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 on patient history (often at least partially reported by a relative) and clinical evaluation, including neurological and neuropsychological assessment, and often it is made by excluding other conditions.

However, researchers are actively working on ways to improve the diagnosis of Alzheimer’s disease, to both increase accuracy and improve earlier diagnosis using imaging and non-imaging biomarkers (e.g., genetics, molecular, biochemical).

In particular, the use of Positron Emission Tomography (PET), in combination with various radiochemicals appears to be a promising tool to visualize both amyloid plaques and neurofibrillary tangles, whereas another imaging technique, called single-photon emission computed tomography (SPECT) appears to be very helpful in differentiating the disease from other brain conditions. A number of molecules measured in the serum or cerebrospinal fluid of affected patients have also been identified as potentially useful in the diagnosis and follow up of Alzheimer’s.

While these and other approaches offer promise to accelerate or improve the diagnosis of Alzheimer’s, more time and research is warranted to assess their accuracy and applicability. As our understanding of the disease grows so does our ability to find new potential treatment approaches and, ultimately, effective new medicines.

“AD research has developed to the point where scientists are looking beyond treating symptoms to addressing the underlying disease process.... NIA [National Institute on Aging] and pharmaceutical companies support treatment clinical trials that are aimed at slowing, delaying, or preventing AD. The advances in our knowledge about the mechanisms and risk factors associated with AD have expanded the types of interventions under study.”

National Institute on Aging\(^6\)
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 has yielded five medicines that provide some symptomatic relief in some cases but has not yet resulted in an approved disease-modifying medicine. (See “Today’s Treatments”.) There are many reasons Alzheimer’s research is so challenging for drug developers. For example:

• As detailed above, progress has been made, but scientists still do not fully understand the underlying causes and mechanisms of the disease, particularly when it comes to separating potential causes from effects of the disease. This makes selection of viable targets for new medicines very difficult.

• The limited utility of current models of the human disease is a huge barrier in preclinical testing of drug candidates.

• The absence of validated non-invasive biomarkers of disease activity and progression, which delays the diagnosis until patients become symptomatic, makes it particularly challenging to evaluate, enroll, follow up, and retain patients in clinical studies. 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, support and contributions by multiple stakeholders – including government, academia, industry, and patient associations – are important to advancing the field as whole. (See next page.)

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 successes to prevent or treat Alzheimer’s disease.
The enormity of the challenges facing Alzheimer’s disease researchers means that no single company, institute, or organization can tackle the disease alone, particularly when it comes to diagnosing and evaluating the progress of the disease. There are many collaborations in the world of Alzheimer’s research; here is just one example:

In 2004 the National Institute on Aging partnered with a group of federal agencies, non-profit organizations, and industry members to launch the Alzheimer’s Disease Neuroimaging Initiative (ADNI) with the goal of identifying the physical changes associated with cognitive changes that may appear within the brain prior to the onset of Alzheimer’s disease, tracking its progression, establishing quality standards for imaging data collection and sharing, and validating biomarkers to be used in clinical trials. ADNI researchers gather imaging, clinical, biological, and neuropsychological data from groups of study volunteers with normal cognitive functions, those with mild cognitive impairments, and Alzheimer’s disease sufferers. Tools such as MRI/PET scans and cognitive testing are used in conjunction with blood and cerebrospinal fluid samples to measure biomarkers and look at changes in the brains of living participants.

Data collected from ADNI is made available at no cost to other researchers to analyze and use when designing Alzheimer’s disease clinical trials and research projects. Initially a five-year study, ADNI is currently NIH’s largest public and private partnership for Alzheimer’s disease research, and similar projects are now underway around the world. This collaborative effort has real-world implications for patients with Alzheimer’s disease, as pharmaceutical companies developing drugs to treat Alzheimer’s disease are able to use ADNI data and methodologies in their clinical trials.
Today’s Treatments

While it is clear that we need to find ways to prevent, treat, or cure Alzheimer’s disease, we have made some progress in controlling its symptoms. Prior to the 1990s there were no medicines for Alzheimer’s. Currently there are five FDA-approved medicines to help manage symptoms in the affected patients, including memory loss, thinking, and reasoning problems. Unfortunately, these medical treatments do not always work, they cannot cure the disease or stop its progression, and when they work their efficacy often wears off over time. However, many experts urge early treatment with these existing medicines to make them most effective in controlling patients’ symptoms before they deteriorate.

“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.”

Alzheimer’s Foundation of America
Setbacks have greatly outnumbered successes in Alzheimer’s drug development. This is in part related to the complexity and challenges of researching this disease as previously discussed, but also simply reflect the nature of drug discovery and development. 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 may provide new information for biopharmaceutical researchers that they can use to build on going forward. Although every discontinued or suspended drug development project is extremely disappointing, progress made in medical research is often incremental, and success rarely happens overnight. It evolves over time as scientists uncover new aspects of the disease and how they apply to the discovery and development of new or better treatments. Setbacks are not dead ends, but rather opportunities for fresh starts.

It is also important to understand that scientific innovation is the cumulative result of successes and failures. Scientific progress and drug development are deeply intertwined: setbacks as well as successes contain valuable lessons for future development research. As the data from a negative outcome is analyzed, the key learnings are applied in the design of new experiments and approaches, until ultimately achieving a successful outcome or proof-of-concept for a new therapy.

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 recent disappointing clinical results of a drug which targeted beta amyloid plaques, the global head of neuroscience drug development at Janssen Research and Development, Dr. Husseini Manji, 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 hell of a lot from this data.”

Another company, Lundbeck, Inc., which has some plaque-targeting drugs in early development, has stated that it is closely watching these studies and those of another high-profile unsuccessful candidate medicine. Lundbeck’s R&D head, Anders Gersel Pedersen said, “We want to have those insights before we embark on big investments targeting” plaques. The company is hoping to

“You are going to learn from every study you do. That will get you to the end of the road eventually.”

William Thies, Chief Medical & Scientific Officer
Alzheimer’s Association
glean information about the types of patients who may respond best to the treatments and how they might be identified. 28

In recent years we have seen a steady stream of drug candidates in development accompanied by a long series of unsuccessful outcomes. As research has intensified we have seen a higher average of potential medicines pulled out of development each year.

Unsuccessful Alzheimer’s Drugs in Development
1998 - 2011

The number of investigational drugs studied for the treatment of Alzheimer’s disease that fail to reach patients each year offers a simple metric of both the difficulty of the endeavor and the commitment of biopharmaceutical researchers to find better treatments for the disease.

An examination of data from the Adis R&D Insight database shows that since 1998, 101 medicines in development have been become inactive and have not received regulatory approval. (See figure above.) Of those, 83 have been definitively discontinued. The “inactive” category includes investigational studies which 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). (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.)
Since 1998 three new medicines for Alzheimer’s were approved, resulting in a 34 to 1 ratio of “failures” to approvals (two other medicines were approved before this timeframe). It should not be concluded that these numbers imply that for every 34 setbacks one new approval will result, but it provides an indication of recent research outcomes. Since 2003, when the most recent Alzheimer’s medicine was approved, there have been 66 unsuccessful projects.

Recent years have yielded a particularly high number of halted projects, with an average of 10 per year in 2006-2011, compared with 5 per year in 2000-2005. Although this report does not examine trends in the number of medicines in development, it is possible that this increase, at least in part, reflects an increase in the number of research projects in the pipeline.

Each of these unsuccessful efforts contributes to shaping the future direction of Alzheimer’s research, by providing much needed data that allow researchers to draw conclusions and make decisions. For example, one project may show some small benefit – although not enough to warrant further study or regulatory approval – so researchers go back to the drawing board to find 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 that such an approach should be abandoned. Regardless of the exact circumstances, all unsuccessful projects are opportunities to learn more about the disease.

Supporting Progress

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

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

David Michelson M.D.
Merck Research Laboratories

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 in order to achieve eventual success against serious diseases and conditions like Alzheimer’s disease.
Continuing to Innovate

There is reason for optimism in the coming years. Nearly 100 medicines are currently in clinical trials or under FDA review for Alzheimer’s and other dementias. The drugs in this pipeline take many different approaches to treating, stopping, reversing, and preventing the disease.

Our grasp of the underlying causes and processes of the disease is growing. Drawing on this knowledge, researchers will have more and more potential lines of attack against Alzheimer’s.

Many biopharmaceutical researchers and companies are profoundly committed to finding treatments that realize the promise of this expanding scientific knowledge to halt or prevent the disease. Researchers are devoting their entire careers to ending the burden of Alzheimer’s disease. Like many of us, they know someone who has suffered from Alzheimer’s, and they have seen the impact it has on patients and families.

In the face of deeply disappointing setbacks, researchers take the findings from the unsuccessful projects and use that new information to step forward and continue their quest. They understand scientific progress and success is built over time, requiring patience and persistence. And they know that treatment with new medicines is likely to be our best tool for preventing and fighting Alzheimer’s disease, so they continue to forge ahead to understand the disease and translate that knowledge into treatments.

As our population ages, Alzheimer’s disease is among the most important diseases to address and conquer. Not only will the cost and resource burden balloon, but the disease will 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.

“For millions of Americans, the heartbreak of watching a loved one struggle with Alzheimer’s disease is a pain they know all too well. Alzheimer’s disease burdens an increasing number of our Nation’s elders and their families, and it is essential that we confront the challenge it poses to our public health.”

President Barack Obama
A note on methodology: Data are drawn from the Adis R&D Insight database which compiles publicly available information on medicines in development. Medicines included were categorized in the database as “suspended,” “discontinued” or “no development reported” for the indication “Alzheimer’s disease”. Only projects in clinical development 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: 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.”
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.”

According to correspondence with 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 quite 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 is less comprehensive before this time. Data are current as of August 8, 2012, but do not include partial year data from 2012.
References


32. D. Michelson, Interview with Pharmaceutical Research and Manufacturers of America, October 2011.

