Alzheimer’s Disease Report

April 2009

Published by:
The FasterCures Philanthropy Advisory Service
FasterCures / The Center for Accelerating Medical Solutions
1101 New York Ave. St., NW, #620
Washington, D.C. 20005
(202) 336-8900
www.philanthropyadvisoryservice.org
The *FasterCures* Philanthropy Advisory Service

**FasterCures / The Center for Accelerating Medical Solutions**

*FasterCures / The Center for Accelerating Medical Solutions* is a nonprofit “action tank” whose mission is to identify and implement global solutions to accelerate the process of discovery and clinical development of new therapies for the treatment of deadly and debilitating diseases. *FasterCures*, as a center of the Milken Institute, is nonpartisan, nonprofit, and independent of interest groups.

Barriers to progress in accelerating cures exist all along the research continuum—from basic research to development, from medical education to medical practice, from investment capital to human capital. *FasterCures* is working to clear the path to faster progress, not just by analyzing barriers, but by overcoming them through action. A force to catalyze systemic change, *FasterCures*:

- Evaluates current systems of disease prevention, research, development, and treatment;
- Identifies barriers to efficiency, effectiveness, and expediency in those systems;
- Creates achievable action plans to improve those systems; and
- Provides seasoned leadership and expertise in implementing those action plans in concert with organizations searching for new medical solutions.

To guide its efforts, *FasterCures* developed a Blueprint for Change focused on the transformation needed in three areas of medical research: research leadership and innovation; research tools and resources; and the medical research environment. The *Philanthropy Advisory Service (PAS)* aims to promote progress in all three areas through more informed philanthropic investment.

**Helping Philanthropists Make Informed Investment Decisions**

The lack of independent, reliable data about nonprofit disease research opportunities is a major barrier to encouraging significant support for such research and to improving the efficiency and productivity of philanthropy. With grants from the Bill & Melinda Gates Foundation and the Pioneer Portfolio of the Robert Wood Johnson Foundation, *FasterCures* has developed the **PAS** to address this problem.

The objectives of PAS include:

- Helping philanthropists align their goals and expectations with the capabilities and approaches of research organizations;
- Identifying gaps in funding for areas crucial to the success of specific disease research efforts; and
- Promoting among potential donors a "continuum of cure" perspective that can help develop cures for deadly and debilitating diseases.

PAS creates an information marketplace to support informed philanthropic investment. It improves the efficiency and productivity of both philanthropists and the nonprofit disease research...
organizations that depend on their support, especially in areas where there are demonstrated funding gaps in research and development.

**Philanthropy Advisory Service Analyst Reports**

PAS provides two types of reports—disease and organization reports.

- **Disease Reports** discuss the burden, progression, and existing treatments for a given disease; highlight priority research areas; and provide an overview of relevant activities in the commercial and nonprofit research sectors. These reports provide a broader understanding of the disease, its toll on the greater society, and any potential products in the pipeline, as well as describe promising research areas. This information establishes the contextual knowledge for readers to consider as they evaluate nonprofit organizations in a specific disease area, particularly with regard to whether an organization is addressing key research areas and challenges.

  PAS develops disease reports using desktop research. Each report is reviewed and validated by a Scientific Advisory Board, or SAB, composed of leading researchers and clinicians in that disease area.

- **Organization Reports** are developed describing the activities of nonprofit organizations involved in disease research. For diseases primarily affecting the developed world, organizations reviewed include those funding research, as well as those providing tools to support research efforts. For diseases primarily affecting the developing world, the organizations reviewed include product development partnerships as well as academic and private research organizations.

  These reports provide detailed information on strategy, research portfolio, management, and financials. They also include an assessment of the organization’s practices according to a set of metrics that FasterCures believes contribute to the acceleration of biomedical research. Readers can use this information together with the context outlined in the disease report as an aid to making philanthropic investment decisions.

  Organization Reports are developed based on information collected in the public domain, augmented by discussions with representatives of the organization, with input from the relevant PAS SAB.
# Table of Contents

**SUMMARY** ........................................................................................................................................................................... 1

**DISEASE BURDEN** ....................................................................................................................................................................... 4
  - OVERVIEW ................................................................................................................................................................................. 4
  - BURDEN ..................................................................................................................................................................................... 4
  - RISK FACTORS ............................................................................................................................................................................ 6
  - BIOLOGY .................................................................................................................................................................................... 7
  - INTERVENTIONS ......................................................................................................................................................................... 10

**RESEARCH** .................................................................................................................................................................................. 13
  - OVERVIEW ................................................................................................................................................................................. 13
  - SCIENTIFIC RESEARCH ............................................................................................................................................................ 13
  - RESEARCH INFRASTRUCTURE .................................................................................................................................................. 28
  - CLINICAL TRIALS ....................................................................................................................................................................... 34
  - FUNDING .................................................................................................................................................................................... 35

**MARKET ANALYSIS** ....................................................................................................................................................................... 37
  - OVERVIEW ................................................................................................................................................................................. 37
  - PRODUCTS .................................................................................................................................................................................... 37
  - MARKET SHARE ......................................................................................................................................................................... 39
  - PIPELINE ................................................................................................................................................................................... 40

**COMMERCIAL PLAYERS** ............................................................................................................................................................... 42
  - OVERVIEW ................................................................................................................................................................................. 42
  - KEY COMPANIES ....................................................................................................................................................................... 43

**NONPROFIT PLAYERS** .................................................................................................................................................................... 47
  - OVERVIEW .................................................................................................................................................................................. 47
  - KEY ORGANIZATIONS ................................................................................................................................................................. 47

**ACRONYMS** ..................................................................................................................................................................................... 50

**GLOSSARY** ..................................................................................................................................................................................... 51

**REFERENCES** .................................................................................................................................................................................. 56
Summary

Disease Definition
Alzheimer’s disease (AD) is the most common form of dementia, characterized by protein deposits in the brain. AD first manifests as memory and learning challenges, then spreads to other brain functions such as reasoning, recognition and the senses. The disease eventually leads to death.

Key AD Statistics for the United States
AD takes a toll on both the health of the U.S. population and its economy. Based on data from the Alzheimer’s Association and the Centers for Disease Control and Prevention, AD’s burden can be evidenced by the following statistics:

- As of 2009, there are 5.3 million cases of AD in the United States;
- New cases of AD in 2009 are expected to reach 449,700;
- In 2006, 72,914 people died from AD;
- AD affects 13 percent of those 65 years of age or older and 40 percent of those 85 years of age or older; and
- AD and other dementia cost the U.S. economy $100-$148 billion per year (including lost productivity).

Current Treatment
Currently, there is no cure for AD. Several treatments are available to delay progression of clinical symptoms for a limited period of time; however, no existing drug addresses the underlying biological causes of the disease. In addition to drugs approved for AD, antipsychotic drugs and non-drug treatments such as physical or music therapies are used to reduce behavioral symptoms.

Research Investment
In 2007, the U.S. government’s investment in AD was approximately $645 million, which was a marginal increase from 2006 but a decrease from the funding levels in 2004 or 2005. There are 264 clinical studies underway for AD, and the National Institutes of Health (NIH) supports 20 percent of all active AD trials, compared to 22 percent for all conditions. Industry sponsors 53 percent of all active AD trials, compared to 33 percent for all conditions.

Key Research Areas
Research efforts are underway in the federal, academic, and commercial sectors to better understand AD in order to develop effective treatments, methods of prevention, and diagnostic tools. Efforts can be categorized according to the following:

- Understanding AD as a disease, including its risk factors, causes, and progression
- Identifying lifestyle factors that contribute to the onset of AD, including the effects of co-morbid disease
Developing methods for diagnosing and monitoring disease progression, as well as treatment efficacy
• Searching for treatments that modify disease progression and its toxic effect or that provide relief against secondary symptoms
• Testing effective methods for delivering patient care

**Challenges**
AD research faces critical challenges, including the following:

• Difficulty in understanding the process of disease onset and development
• Limited sensitivity of diagnostic tools, which limits early diagnosis and the effective measurement of treatment effect and disease progression
• Difficulty showing efficacy in small-scale and short-term trials

**Key Nonprofit Research Funders**
There are five major nonprofit organizations funding AD research, outlined below.

<table>
<thead>
<tr>
<th>Name</th>
<th>Annual Research Funding</th>
<th>Research Funding/Expenses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's Association</td>
<td>$25.6M</td>
<td>28%</td>
</tr>
<tr>
<td>American Health Assistance Foundation</td>
<td>$5.2M</td>
<td>20%¹</td>
</tr>
<tr>
<td>Cure Alzheimer’s Fund</td>
<td>$2.4M</td>
<td>82%</td>
</tr>
<tr>
<td>Alzheimer’s Drug Discovery Foundation</td>
<td>$2.1M</td>
<td>59%</td>
</tr>
<tr>
<td>John Douglas French Alzheimer’s Foundation</td>
<td>$1.4M</td>
<td>75%</td>
</tr>
</tbody>
</table>

**Key For-Profit Players**
There are five drugs on the market that treat symptoms of AD, and there are 74 industry projects in clinical development.

---

¹ AHAF funds research in three diseases including AD. The figure shown here includes only research grants for AD. Its total research funding, including AD, glaucoma, macular degeneration, is larger and amounts to 37 percent of total budget.
AD drugs on the market (companies)2

- Aricept (Eisai, Pfizer)
- Namenda (Merz, Forest Labs., Lundbeck)
- Razadyne (Johnson & Johnson, Shire)
- Exelon (Novartis)
- Cognex (Sciele)

Companies with largest AD pipelines3

- Pfizer/Wyeth (10)4
- Roche/Genetech/Memory (8)
- Merck & Co. (6)
- Eli Lilly (4)
- GlaxoSmithKline (4)
- Elan (3)

---

1 Sorted in descending order of the drug’s revenue in the United States, includes both drug developers and distributors, globally.

2 Ranked by the size of pipeline. Number of compounds applicable to AD in parentheses.

3 Not including the co-development agreement with Medivation for Dimebon, in Phase 3 trials.
Disease Burden

Overview
AD is a neurodegenerative disease, most common in older people. It seriously impairs a person’s ability to conduct the activities of daily life and eventually results in death as communication among nerve cells is disrupted and nerve cells are lost.

Because age is one of the most important risk factors for AD, the burden of AD will increase with longer life expectancies and the aging of the baby boomers. It is estimated that by 2050, 11-16 million people will suffer from the disease in the United States, which will lead to significant population and economic burdens. Awareness of this growing problem is increasing, due to awareness efforts of nonprofit organizations and national advocacy efforts, such as the Alzheimer’s Study Group, which calls for a national plan to cope with the burden of AD.

Burden

Population Burden
AD is the most common form of dementia, accounting for two-thirds of all cases. There are two types of AD: early-onset familial and late-onset. Early-onset familial AD usually occurs at middle age, is less frequent, and is driven by genetic factors. Late-onset AD primarily affects people aged 65 years or older and accounts for 90 to 95 percent of all AD cases; no single cause is identified, although age and various risk factors affect onset.

In 2007, the Alzheimer’s Association estimated that there are 5.1 million AD patients in the United States. This number includes 200,000 patients younger than age 65 who suffer from early-onset AD. Thirteen percent (4.9 million) of the population aged 65 years and older is estimated to have AD. In 2009, this number has increased to a total of 5.3 million patients, including 200,000 patients under age 65, and the prevalence is expected to increase to 6.5 million by 2025 (Figure 1).
The 85 and over age group accounts for 45 percent of AD patients, the 75 to 84 age group for 49 percent, and the 65 to 74 age group for the remaining 6 percent. Since the 85 and over age group accounts for only 15 percent of the senior population, 40 percent of this age group suffers from AD.

As life expectancies lengthen and the baby boomers age, the incidence of AD is expected to increase by 2.1 percent compound annual growth rate (CAGR) during the first half of the century (Figure 2). The mean age of onset of dementia is estimated to be 80 years.

In terms of DALYs (Disability-Adjusted Life Years), the burden of AD and other forms of dementia in the United States was 1.1 million, or 2.8 percent of total DALYs lost, in 2002. According to the Centers for Disease Control and Prevention (CDC), AD is the 7th most common cause of death in the United States, accounting for 2.8 percent of total deaths in 2005. Deaths attributed to AD grew from 14,112 in 1991 to 72,914 in 2006, which translates into a compound annual growth rate (CAGR) of 12 percent. Estimates on survival after diagnosis vary but range from four to ten years.

**Economic Burden**

NIH estimated the annual cost of AD during the 1990s to be more than $100 billion. The bulk of the cost was borne by the Centers for Medicare & Medicaid Services (CMS) through Medicare and Medicaid reimbursements; AD’s growing prevalence will increase the pressure on the government’s budget. The Alzheimer’s Association estimates that the cost of AD and other dementia in 2005 amounted to over $148 billion. Table 1 provides a further breakdown of this cost.

**Table 1: Estimates of Annual Expenses for AD and Other Dementia**

<table>
<thead>
<tr>
<th>Expense Item</th>
<th>Annual Expense</th>
<th>Year of Estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare costs</td>
<td>$91B</td>
<td>2005</td>
</tr>
<tr>
<td>Medicaid reimbursements for nursing home care</td>
<td>$21B</td>
<td>2005</td>
</tr>
<tr>
<td>Business cost related to caregivers</td>
<td>$36.5B</td>
<td>2002</td>
</tr>
</tbody>
</table>

**Source:** Alzheimer’s Association (2009).

Because most AD patients are senior citizens, costs to Medicare and nursing home costs paid by Medicaid account for a significant portion of AD-related costs. Costs related to caregiver absenteeism, employee replacement, related productivity loss, and employee assistance programs are accounted for in the business costs related to caregivers. The impact of AD on caregivers is significant, and it goes beyond the productivity cost laid out on Table 1. Caregivers often suffer from depression, substance use, or physical illnesses resulting from emotional and physical stress.

---

5 According to the Alzheimer’s Association, this number may actually be an underestimation because of coexisting conditions in the senior population.
AD and other dementia also incur additional out-of-pocket medical costs. In 2004, the Alzheimer’s Association estimated that seniors with dementia spend 29 percent more in out-of-pocket medical expenses than those without dementia.

The development of disease-modifying drugs for AD is expected to reduce the disease burden, though not necessarily in the short term, since disease-modifying drugs, especially those that act only in very early stage of the disease, may not reverse already inflicted neurodegeneration. This highlights the importance of symptomatic treatment and need for a treatment that works for patients with more advanced disease, as well as other support mechanisms.

**Risk Factors**

Multiple risk factors have been linked to AD. **Age** is the most obvious, and the risk of developing AD is estimated to double every five years starting at age 65. Lower **educational attainment** also has been linked with higher risk of developing AD.

**Genetic factors** also play a role in determining whether a person develops AD. Many of the genes identified as being associated with AD are related to the production or aggregation of beta-amyloid, and several of those genes have been linked to early-onset familial AD. For these dominantly inherited mutations, clinicians routinely perform genetic testing. Many possible susceptibility genes for late-onset AD have been discovered, but the ApoE gene is the only established genetic risk factor of late-onset AD. Individuals with a pair of the ApoE4 version of the gene are estimated to have a 50- to 90-percent chance of developing AD by age 85, compared to 20 percent for the general population. The ApoE2 version of the gene may actually prevent AD. However, susceptibility genes are not used for diagnosis since genetic factors alone do not guarantee onset of the disease. Clinical practice as to whether to share ApoE type information with patients varies. In addition, recent research efforts have identified additional genes associated with the risk of late-onset AD, thus making genetic testing even more complex.

**Medical conditions** such as head trauma, diabetes, depression, high cholesterol, and cardiovascular diseases (including stroke) and other risk factors (such as a high level of the amino acid homocysteine) also are associated with a higher risk of developing AD.

Evidence from association studies suggests that strategies for healthy aging—keeping socially and intellectually active, exercising regularly, quitting smoking, and consuming alcohol in moderation—may offer protection against developing AD.

---

6 ApoE protein plays a role in the transportation of cholesterol and is associated with the development of beta-amyloid plaques.
7 For more details, see the Research section of this report.
Biology

Cause

AD is caused by irreversible loss of neurons (Figure 3) and results in “a progressive and fatal neurodegenerative disorder manifested by cognitive and memory deterioration, progressive impairment of activities of daily living, and a variety of neuropsychiatric symptoms and behavioral disturbance” (Cummings, 2004). First observed in 1906, AD is characterized by the presence of large amounts of plaques of beta-amyloid (Figure 4) and tangles of tau protein in the brain biopsy.  

Beta-amyloid is formed when amyloid precursor protein (APP), an important protein for neuron growth and repair, is severed by enzymes. Tau protein is usually found inside the axon, the part of the nerve cell that serves as a channel to transmit neuronal signals, and assists in the delivery of nutrients to the neuron (Figure 5). When tau protein tangles, the delivery of nutrients is disrupted and the neurons die.

Plaques, tangles, and slight deterioration of memory and learning also may be noticed in a normally aging brain with no apparent symptoms of AD. However, experts increasingly suspect that these are cases of early AD, before the patient is symptomatic.

While the direct cause of AD is unknown, several events are thought to trigger the degenerative process:

- Increased free radical formation
- Excitotoxicity
- Inflammatory response

The degenerative process is believed to begin even before plaques form in the brain, and the disease progression begins even before symptoms appear. Researchers have observed that the brains of patients in the early stages of AD are active in more dispersed areas than are the brains of normal individuals when performing a given task, suggesting that the brain is initially compensating for the loss of neurons in specific parts of the brain by leveraging cells in other healthy parts of the brain. This may explain why noticeable loss in brain function is preceded by an initial period of mild and stable decline.

---

8 Please consult the glossary toward the end of this report for explanation of scientific terms.
9 Note that whether or not the tangles and plaques are actually toxic or result from the body’s reaction to other toxicity is still unclear. Recent studies in animal models have proved that beta-amyloid plaques negatively impact neurons, although why they are formed and whether they are the main cause of AD has not been determined.
10 Beta amyloid–associated AD is comprised of 42 amino acids, so it is also referred to as beta-amyloid 1-42. Three enzymes sever APP: alpha, beta, and gamma secretases. Beta-amyloid 1-42 is formed through the action of beta- and gamma- secretases.
11 Further explained in the discussion of treatments.
Multiple hypotheses have been put forth to explain the root cause of AD and the sequence of events that lead to degeneration. Currently, the dominant theory is the **amyloid cascade hypothesis**. According to this hypothesis, an excess of beta-amyloid in the brain, whether due to overproduction as in the case of familial AD, or failure to break down the excess, triggers the events that result in neuron death or degeneration. This in turn produces critical neurological chemicals that further deteriorate nerve function. Beta-amyloid increasingly is perceived as the key cause of the disease, but the sequence of events that lead to the disease is still debated.

Another theory is the **tau hypothesis**, which points to an imbalance among the different subtypes of tau protein and the development of toxic functions, causing the malfunction of tau protein. This leads to the loss of microtubules, the structures in the axons that serve as skeletons and assist the movement of mitochondria, and to an increase of tau tangles. Ultimately, this leads to neurodegeneration due to starvation.12 Another hypothesis asserts that the destruction of the neurons that produce **acetylcholine**, a neurotransmitter critical to memory formation, is the leading cause of AD. Although later research showed that the deficit of acetylcholine does not occur during the early stages of the disease, this hypothesis has led to the development of several AD drugs currently in use to delay the disease process and provide symptomatic relief.

**Progression**

AD progresses through various regions of the brain. It first affects the entorhinal cortex, spreads to the hippocampus, to which it is connected, then to the cerebral cortex, and ultimately to the whole brain (Figure 6). The appearance of symptoms follows the sequence by which the brain areas are affected and their respective functions. AD first affects memory, learning, and language; then reasoning, recognition, sensory processing, and conscious

---

12 Tau protein is associated with multiple neurodegenerative diseases that share similar symptoms.
thoughts; and finally mobility and the senses.

Multiple staging systems have been developed, but the most commonly used in the clinical setting is the generic model of mild, moderate, and severe, although sometimes a patient may not clearly fall into one stage (Table 2). Approximately 50 percent of AD patients are first diagnosed when they are in the moderate stage. The Mini-Mental Status Examination (MMSE), a test covering various aspects of mental function, is often used in conjunction with clinical observation and other factors to determine the stage of AD.

The following secondary symptoms appear as the disease progresses:

- Depression: 25 to 50 percent of patients
- Agitation: 50 to 70 percent of patients
- Psychotic symptoms (e.g., delusions, hallucinations): 30 to 60 percent of patients

Table 2: Stages and Progression of Clinical AD

<table>
<thead>
<tr>
<th>AD Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Memory loss</td>
</tr>
<tr>
<td></td>
<td>Confusion about the location of familiar places</td>
</tr>
<tr>
<td></td>
<td>Taking longer to accomplish normal daily tasks</td>
</tr>
<tr>
<td></td>
<td>Trouble handling money or paying bills</td>
</tr>
<tr>
<td></td>
<td>Poor judgment leading to bad decisions</td>
</tr>
<tr>
<td></td>
<td>Loss of spontaneity and sense of initiative</td>
</tr>
<tr>
<td></td>
<td>Mood and personality changes, increased anxiety</td>
</tr>
<tr>
<td>Moderate</td>
<td>Increased memory loss and confusion</td>
</tr>
<tr>
<td></td>
<td>Shortened attention span</td>
</tr>
<tr>
<td></td>
<td>Problems recognizing friends and family members</td>
</tr>
<tr>
<td></td>
<td>Difficulty with language and numbers</td>
</tr>
<tr>
<td></td>
<td>Difficulty organizing thoughts and thinking logically</td>
</tr>
<tr>
<td></td>
<td>Inability to learn new things or cope with new situation</td>
</tr>
<tr>
<td></td>
<td>Restlessness, agitation, anxiety, tearfulness, and wandering</td>
</tr>
<tr>
<td></td>
<td>Repetitive statements or movements and muscle twitches</td>
</tr>
<tr>
<td></td>
<td>Hallucinations, delusions, suspiciousness, paranoia, irritability</td>
</tr>
<tr>
<td></td>
<td>Loss of impulse control (e.g., inappropriate undressing)</td>
</tr>
<tr>
<td></td>
<td>Perceptual-motor problems (e.g., setting the table)</td>
</tr>
<tr>
<td>Severe</td>
<td>Loss of ability to communicate</td>
</tr>
<tr>
<td></td>
<td>Failure to recognize loved ones</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Seizures, skin infections, difficulties swallowing</td>
</tr>
<tr>
<td></td>
<td>Groaning, moaning, or grunting</td>
</tr>
<tr>
<td></td>
<td>Increased sleeping</td>
</tr>
<tr>
<td></td>
<td>Lack of bladder and bowel control</td>
</tr>
</tbody>
</table>

Source: National Institute on Aging.

For example, the Clinical Dementia Rating Scale or the Global Deterioration Scale.
Most AD patients die of complications that develop as the body stops functioning properly. A common cause of death for AD patients is aspiration pneumonia, resulting from an inability to properly swallow food and liquid.

**Interventions**

**Diagnostics**

Clinical testing and observation is used to diagnose AD. Though a strict and definitive diagnosis can only be made after autopsy, the accuracy of current diagnoses ranges from 85 to 90 percent, with each diagnosis associated with a certain degree of confidence, such as “probable” or “possible.”

According to criteria set by the American Psychiatric Association, a diagnosis of AD should be predicated on observations of the following symptoms in the patient:

- Memory impairment and at least one additional cognitive impairment
- Impaired functioning and functional decline
- Gradual onset and continuing cognitive decline
- Cognitive deficits not due to other causes

Multiple clinical tests have been developed to measure mental decline by asking patients to memorize and associate certain words as well as to complete simple mathematical calculations or to draw an item that can test multiple brain functions. Such tests include the MMSE, the Clock Drawing Test, or the Blessed Information-Memory-Concentration test.

Once mental decline is confirmed, standard medical tests are conducted to dismiss other potential causes of dementia, such as stroke, Parkinson’s disease, or tumors. Such tests include blood tests and neurodiagnostic tests such as brain screening.

Mild Cognitive Impairment (MCI) differs from AD, because it affects only memory, without functional decline, and patients cannot be called “demented.” Scientists continue to debate whether MCI is actually an early stage of AD. Some studies have shown that MCI patients are three times more likely to progress to AD than those without MCI, and autopsy reports of MCI patients have shown plaques and tangles that are signatures of AD. At the same time, as many as 50 percent of MCI patients do not progress to AD, at least within six years, and some even show improvement in memory over time.
Treatments

Table 3: Drugs for the Treatment of AD

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Stage of Disease Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Donepezil</td>
<td>X</td>
</tr>
<tr>
<td>Galantamine</td>
<td>X</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>X</td>
</tr>
<tr>
<td>Tacrine</td>
<td>X</td>
</tr>
<tr>
<td>Memantine</td>
<td>X</td>
</tr>
</tbody>
</table>

Source: Dash (2005); Alzheimer’s Association.

While there is no cure for AD, there are treatments to slow the disease’s symptomatic progression. Lifestyle changes such as exercise and diet are also suspected to prevent or delay the disease. Currently, there are five U.S. Food and Drug Administration (FDA)-approved drugs for the treatment of AD (see Table 3). All of the drugs except memantine are cholinesterase inhibitors. These drugs work by preventing the dismantling of acetylcholine, a neuromodulator needed for learning, memory, and judgment; preventing its decomposition in the brain is believed to slow mental degeneration. Tacrine was the first of this drug class, but it has been largely replaced by the others because of its side effects. Cholinesterase inhibitors are believed to delay the disease process by 6 to 12 months, but the symptoms eventually worsen with the further destruction of neurons.

Memantine is known to interfere with the action of glutamate, a neurotransmitter that increases the calcium level in the neurons and affects cell communication. If there is an excess of glutamate and associated receptors, the ions in the cells become unbalanced, which can lead to the death of neurons, an effect called excitotoxicity. By interfering with the action of glutamate, memantine reduces this toxic effect of ion imbalance.

Antidepressants and antipsychotic medications, are often prescribed to treat secondary symptoms. FDA disapproves of this practice, but some clinicians assert that the use of antipsychotic medications, especially the atypical antipsychotic agents, may be beneficial and sometimes necessary. Recent studies, however, suggest that the use of atypical antipsychotic drugs may present more risk than benefit, thus supporting nonpharmacologic treatments such as exercise as an alternative.

---

14 Called NMDA receptors.
Research

Overview
In the past 20 years, much progress has been made in understanding AD. Today, scientific advances are simultaneously occurring in basic biology and treatment research. Key areas of research include disease etiology, risk factors, biomarker development, treatment and cure development, care delivery, and the role of nutrition. Many tools facilitating research, such as collections of tissue specimens, animal models, and data standards, are also in development. Yet the field still faces many challenges and requires more investment.

In 2007, NIH invested $645 million, or two percent of its total budget of $28 billion, in AD research. As of February 2009, there are 264 ongoing AD clinical trials. Clinical research on AD is characterized by a relatively higher share of Phase 1 trials, higher involvement of industry, and more trials testing drugs and behavioral measures.

Scientific Research

Summary
Table 4 summarizes the major areas of scientific research in AD and areas where more investment is required to overcome challenges and accelerate research. The areas of current research and the challenges were identified and prioritized through consultation with FasterCures’ PAS Scientific Advisory Board for AD.

<table>
<thead>
<tr>
<th>Table 4: Major Area of Scientific Research and Challenges in AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research continuum</strong></td>
</tr>
</tbody>
</table>
| Etiology | • Investigating the roles and production of beta-amyloid and abnormal tau protein in disease progression  
• Understanding changes in mitochondria and other pathologic events  
• Elucidating genetic and environmental risk factors  
• Understanding mild cognitive impairment as a presymptom | • Lack of understanding of the precise cause, progression, and risk factors, which is a fundamental obstacle to developing interventions  
• Limited understanding of the blood brain barrier and how AD affects it, which limits the development of drugs that can safely access the brain |
| Prevention | • Investigating the influence of lifestyle choices on disease onset  
• Understanding the preventive potential of specific nutrients and treatments for other medical conditions | • Limited research on healthy aging and the very old, which can lead to prevention tools  
• Insufficient validation in larger studies of the impact of lifestyle interventions |
<table>
<thead>
<tr>
<th>Research continuum</th>
<th>Current research foci</th>
<th>Challenges or areas requiring investment</th>
</tr>
</thead>
</table>
| Diagnosis           | • Identifying specific markers for diagnosis and disease monitoring, including imaging and measuring protein levels in the cerebrospinal fluid and blood  
• Alzheimer’s Disease Neuroimaging Initiative as an integrated effort to identify markers for different purposes | • Lack of biomarkers, which is an impediment to developing diagnostics and to understanding disease progression and treatment effects  
• Limited understanding of the circumstances under which potential biomarkers change, which limits their usefulness  
• Existing clinical measures have limited capacity to assess disease progression, making it difficult to detect efficacy signals  
• Diagnostics, in general, are less of a proprietary source of profit than are therapeutics, making it difficult to secure funding |
| Treatment           | • Developing strategies focused on lowering toxic beta-amyloid levels  
• Finding ways to reduce abnormal tau  
• Exploring approaches to enhancing mitochondria activities  
• Improving symptom management | • Relatively limited investment on treatment strategies beyond the two hallmarks of AD, beta amyloid and abnormal tau  
• Lack of a systemic or multi-target approach, which may be more effective given the complex nature of the disease  
• Limited efforts in multidisciplinary and cross-disease collaboration, despite the commonalities of AD with other neurodegenerative diseases  
• Reduced interest in symptomatic drugs, although patients without early diagnosis will continue to need them even after disease-modifying drugs are developed  
• Difficulties in demonstrating efficacy in clinical trials, adding complexities to drug development process |
| Delivery            | • Enhancing technology/tools for caregiving  
• Improving caregivers’ quality of life  
• Exploring care provision through interdisciplinary teams of providers | • Need for efforts to improve care delivery, including research on the impact of physician behavior, symptom management, and nursing care on patient outcome |

**Source:** FasterCures.

### Disease Understanding

**Key areas of research:**

- Beta-amyloid production and its effects on the brain  
- Abnormal tau protein and its effects on the brain  
- Changes in mitochondria  
- Sequence of pathologic events  
- Risk factors  
- Prodromes such as mild cognitive impairment

One of the major challenges in AD research is that there is insufficient understanding of its precise cause and progression, or of its risk factors. While scientists have been able to identify multiple targets that could potentially affect the course of the disease, the sequence of pathways that lead to the onset of AD or the
critical step that leads to neurodegeneration is yet to be fully understood. For example, the role of ApoE—the gene consistently reported as being a risk factor for AD—in the disease process is yet to be clearly understood. Clinical trials suggest that supporting the mitochondria’s function is an effective strategy to treat AD, but scientists do not yet understand why this strategy is effective and how benefits can be maximized.

Much of the research on AD etiology and pathogenesis starts with a specific hypothesis of AD genesis and strives to discover the causal relationships among AD processes in order to find new paths for intervention. Much research also focuses on the basic biology of the brain and MCI.

In addition to the current areas of research focus, scientists point out that better understanding is needed of the blood-brain barrier—the mechanism through which the brain protects itself against potentially harmful agents in the blood. For diseases of the central nervous system, this mechanism often is an important factor that needs to be understood before treatments can be designed. Whether and how the blood brain barrier changes in AD, how it affects the disease, and whether it has implications for treatment are areas where more research is needed to devise more effective treatment strategies.

The following sections outline further details on the major areas of research focused on understanding the underlying causes—etiology—of AD.

**Beta-amyloid production and its effects on the brain:** Beta-amyloid, one of the two hallmarks of AD, is a protein that has been long researched. Scientific study of the protein focuses on its role and effects in the brain, as well as its production and clearance in the brain.

While initial research has been focused on the plaques of beta-amyloid, scientists now think that the protein is toxic in its soluble form. High levels of beta-amyloid are thought to interfere with the generation of new neurons, affect the ion balance and cell membranes, and increase free radicals and inflammation. Scientists are investigating whether other factors might exacerbate the toxic effects of beta amyloid. At the same time, scientists are investigating the role of beta-amyloid in normal brains, including its role in improving memory and learning at low concentration, as well as the implications of the presence of protein plaques in clinically normal elderly populations.

The production and removal of beta amyloid in the brain is another important area of research. Scientists are trying to understand how beta and gamma secretases, the two enzymes involved in the production of beta-amyloid, are formed, what affects their levels, and how they move to the appropriate sites to process APP to produce beta-amyloid. Other research is focused on which enzymes are involved in degrading beta-amyloid; how microglia, a type of immune cell present in the brain, removes the protein; what factors affect the clearance mechanism; and whether there are any abnormalities in this mechanism in AD patients. Another related area of research focuses on how the level of receptors that sort and recycle proteins contributes to the disease process, as they are also related to the ApoE protein.

**Abnormal tau protein and its effects on the brain:** Abnormal tau protein is the other hallmark of AD. Recent research indicates that abnormal tau may be the main reason for neuronal loss, through
the destabilization of microtubules, which assist with the movement of mitochondria in the axon. Research is focused on the specific process of abnormal tau formation, differences in the various subtypes of abnormal tau, and the stage at which toxicity develops.

Scientists are researching the impact of abnormal tau beyond neuronal death, including the impact on dendritic spines that are involved in synaptic transmission, mitochondria abnormalities, and resistance to programmed neuronal death. Animal studies have shown that some of these effects can be reversed and lead to some improvement in clinical manifestation of the disease, even when neuron death cannot be prevented.

**Changes in mitochondria:** How AD affects mitochondria in the neuron is another area of research. Mitochondria are the energy providers of cells, and interference with their normal function and movement along the axon may lead to starvation of the neuron. Research on mitochondria is likely to advance in the near future, as a drug candidate targeting the mitochondria showed positive clinical effects in trials, confirming the importance of mitochondria in the disease process.

Research on mitochondria includes the impact of abnormal tau on the mobility of mitochondria, and the impact of beta-amyloid, which is thought to increase the reactive oxygen molecules within mitochondria. Scientists are investigating other factors that may affect mitochondrial functions, including the impact of enzymes that are found in high levels in AD patients and the influence of ApoE genotype in mitochondria abnormality. In addition, genetic factors specific to mitochondria are thought to be associated with AD.

**Sequence of pathologic events:** Researchers believe that the two hallmarks of AD—beta-amyloid and abnormal tau protein—are closely related and that their levels affect each other. Recent studies suggest that an increase in beta-amyloid precedes abnormal tau formation; however, neurodegeneration is more closely related to the level of abnormal tau. Therefore, it is possible that both mechanisms are implicated in disease onset, and efforts are underway to identify mechanisms affecting both factors.

**Risk factors:** Research on risk factors can reveal the cause and mechanism of disease. Risk factors for AD need further research, especially how the interaction among risk factors affects the overall risk of developing AD. Also, the impact of confounding risk factors needs to be clearly understood. For example, the impact of ethnicity and metabolism on AD risk often are difficult to differentiate. Current research on risk factors can be categorized into genetic risks, demographics, and other medical conditions.

Regarding **genetic risk factors,** three mutations that cause the inherited form of AD have been identified. ApoE is the only genetic factor consistently identified as significantly increasing the risk for developing the late-onset form of the disease. Research is ongoing to understand the mechanism through which the ApoE4 allele increases the risk of AD. In addition, multiple genome-wide association studies have been recently completed or are in progress to identify other susceptibility genes for the late-onset AD.
Scientists are also looking for demographic risk factors. Some epidemiological studies suggested that women have a higher incidence of AD, and the impact of hormone replacement therapy on cognitive function has long been researched. However, the results to date have been inconclusive, with some research even suggesting that some hormone replacement therapy may increase the risk of dementia. At the same time, laboratory studies are ongoing to understand the effect of sex beyond hormones in the risk of AD. Research on the risk of AD conferred by ethnicity is just emerging. Scientists are studying how different factors of cognitive impairment, e.g., social engagement or perceived discrimination differentially affect ethnic minorities. Efforts to increase the participation of African Americans in AD research are another area of focus.

Researchers also are examining how other medical conditions are contributing risk factors for AD. Diabetes, hypertension, stroke, high cholesterol, and abnormality in LDL receptors—cell surface receptors that assist the absorption of low-density lipoprotein—are thought to be risk factors for AD and MCI. Research results are emerging on how the timing of these conditions affects the risk of dementia, the mechanism through which risks are increased, and how management of these conditions reduces the risk of or affects the pattern of AD. Also, small-scale studies have demonstrated positive effects of intranasal insulin and oral diabetic drugs in AD, although they need to be replicated in larger trials. In addition, head trauma is being studied as a factor that increases the risk of AD.

**Prodromes:** While MCI increasingly is accepted as a prodrome (i.e., presymptom) of AD, it is yet to be established as a distinct disorder with clearly defined criteria, as it is diagnosed based only on cognitive symptoms. Recent studies have tried to estimate the prevalence of MCI patients as well as the share of patients who later develop AD. Efforts are being made to define the characteristics of MCI patient groups with different prognoses based on criteria such as baseline cognition and age. In addition, recent studies suggest that depression may be another potential prodrome of dementia, and mild motor impairments are also associated with MCI or dementia.

**Other:** In addition to the major research areas outlined above, scientists have observed an abnormal initiation of cell cycle in the neurons of AD patients, possibly associated with neurodegeneration and cell death; research is ongoing to better understand this mechanism. Inflammation is another phenomenon observed in AD patients, and scientists are studying its role in the disease process. Other studies are focused on how microglial cells and inflammatory responses are affected by beta-amyloid. Another area of research is neurovascular health, as AD patients’ brains seem less able to develop new blood vessels, and beta-amyloid is not removed from the brain properly, possibly because AD patients produce less of the proteins needed to transport beta-amyloid from the brain to blood vessels. In addition to these factors of disease progression, scientists are exploring how the brain compensates for neurons once they are lost and how that process is impaired in animal models of AD.

**Prevention**

<table>
<thead>
<tr>
<th>Key areas of research:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle</td>
</tr>
<tr>
<td>Antioxidants</td>
</tr>
<tr>
<td>Other nutrients and drugs</td>
</tr>
</tbody>
</table>

Identifying lifestyle risk factors for AD and nutritional strategies that can reduce risk is another major area of research, especially in the context of prevention. Current research
primarily focuses on the impact of lifestyle factors and nutrition. These findings could have significant public health implications.

Given that aging is the single most important risk factor for AD, scientists point out that delaying the aging process provides an important avenue of intervention, and the strategy may be effective in maintaining cognitive health even without understanding the disease mechanism itself. As such, increasing research on the oldest old (age group 85 or 90 and above) is needed to understand what factors contribute to healthy aging and reduce the risk of AD. In 2007, the Alzheimer’s Association and CDC developed a national roadmap for a healthy brain, which identified research and public health strategies. The National Institute on Aging (NIA) has plans to investigate the genetics of health aging, focusing on individuals more than 100 years of age. Another topic that could generate insight into AD is the genetics of premature aging, which could lead to identification of prevention tools. However, more investment is needed in these research areas.

Another area requiring investment is validation of lifestyle interventions that are thought to provide protection against the disease. Research to date has identified multiple lifestyle measures that can be beneficial in preventing or delaying disease onset, as surveyed in the next section. However, most of these findings are based on small trials or observational studies, and results have not been consistent in some cases. Therefore, validating their impacts through larger trials is crucial in turning the outcome of these studies into public health measures.

The following sections outline the major areas of ongoing prevention research.

**Lifestyle:** Researchers are investigating the impact of lifestyle on AD risk. Association studies have shown that a heart-healthy diet and regular exercise may reduce the risk of AD. For ApoE4 carriers, tobacco use in midlife was found to increase the risk of AD, and the ill-effects of tobacco were exacerbated by alcohol use. Marital status, neuroticism, and lifetime mental activities also were shown to impact the risk of AD. With increasing evidence suggesting that lifestyle factors influence AD risk, scientists are searching for lifestyle interventions that may prove effective and provide more immediate returns. However, the effectiveness of such interventions is yet to be demonstrated in large clinical trials, and demonstration of such results is needed before implementing public health measures.

**Antioxidants:** The benefits of omega-3 fatty acids to the nervous system and their potential to reduce the risk of developing AD have been the focus of research for some time. In addition to finding that some omega-3 fatty acids encourage the development of networks among neurons, and a high-fat diet without omega-3 fatty acids increases beta-amyloid and tau levels in mice, some clinical studies indicate that omega-3 fatty acids may slow disease progression in very early AD patients. Scientists also are conducting research on whether past omega-3 fatty acid intake affects AD risk. Other vitamins have been studied for their potential to prevent or slow disease progression, including vitamins A, B, C, E, folic acid, alpha lipopic acid, and coenzyme Q. However, conclusive clinical benefit in slowing cognitive decline and treating AD was not been demonstrated.

**Other nutrients and drugs:** In addition to antioxidants, other nutrients and commonly used drugs have been studied for their potential preventive effects, including curcumin, ginkgo biloba, and
caffeine, though definitive effects in humans are yet to be demonstrated. Drugs examined for preventive potential include aspirin and an osteoporosis drug for women. Restriction of calorie intake is another strategy that has been explored, based on demonstrated reduction of cognitive deficit in mice placed on restricted diets.

**Diagnostics**

A crucial problem in the diagnosis of AD is that there are no definitive biomarkers for diagnosis or measurement of disease progression. A biomarker is a specific biological trait, such as the level of a certain molecule, protein, or enzyme in the body that can be measured to indicate the progression of a disease or condition. Currently, clinical examination is the standard method of diagnosing AD and assessing its progress. However, autopsy studies estimate that clinical diagnosis of AD is inaccurate in 10 to 15 percent of cases—and such diagnosis is difficult to access in primary care settings. Clinical measures of disease progression also are insufficient. It is difficult to measure the changes in cognition over time, especially in the early stage of the disease. Understanding whether computerized measures have predictive values in assessing disease progression and how they can be used in treatment needs further research.

More importantly, scientists believe that by the time a clinical diagnosis of probable AD is possible, a sizeable number of neurons already have been lost. Also, new treatments in development, which focus on removing the beta-amyloid that many scientists consider to be the potential cause of AD, did not show any reversal of symptoms in patients with clinical diagnosis. One of the possible reasons for such a failure is that the treatment may need to target patients in an earlier stage of the disease. Identifying those patients is challenging without reliable markers that can detect very early, preclinical disease. Based on recent progress in biomarker research, scientists are suggesting that new diagnostic criteria are needed. Recent research suggests that it might be possible to combine an early and significant episodic memory impairment with at least one abnormality in biomarkers as a new diagnostic criteria, although this needs to be further validated and optimized in additional studies.

Lack of definite biomarkers also makes it more challenging to measure the efficacy of treatments in development, forcing investigators to rely on the intervention’s effect on symptoms in the study group when compared to the control group. However, the disease courses experienced by control groups taking placebos are not necessarily consistent, in part because such trials are of insufficient size and duration to determine true effects. Larger and longer trials with more frequent examination and minimal language variance are needed, but entail higher costs. Identifying biomarkers for use in clinical trials would facilitate the measurement of treatment effects as well as aid in selection of trial participants, thereby reducing costs and improving the accuracy of clinical trials.
In addition to defining the most relevant biomarkers it will be critical to understand the conditions under which the markers change, the implication of such changes, and their importance as they relate to a patient’s risk factors. Research in these areas will foster better understanding of the patient’s status and inform therapeutic choices. For example, understanding how biomarkers change when MCI patients progress to AD and how to prevent such conversion would greatly reduce the disease burden.

Clearly defined biomarkers can facilitate efficacy measurement in clinical trials, allow for smaller trial sizes, enable targeted trials based on clinical profiles, and test for preventive measures if surrogate markers that measure the risk of the disease are developed. Clinical studies suggest that the late-onset AD patient pool is not homogeneous, with varying degrees of disease progression and reactions to treatments. For example, ApoE4 status, profiles of tau, and beta-amyloid levels may affect treatment efficacy and prognosis. Also, some people develop significant AD-like pathology in the brain but do not develop dementia. Reliable biomarkers would enable scientists to distinguish among such groups and develop treatments accordingly.

Despite the importance of research on biomarkers, attracting funding is challenging. Biomarkers are an enabler of other research that benefit the whole field, rather than rewarding specific individuals or organizations. Also, it is an area where the use of a set of standard markers is important to enable comparisons across the field. Thus, the precompetitive nature of biomarkers makes it difficult to secure adequate funding. Even for the Alzheimer’s Disease Neuroimaging Initiative (ADNI), a high-profile project funded through a public-private partnership, attracting adequate funding is a challenge, which highlights the need to expand funding for pre-competitive areas. In addition, securing funding for imaging and device research is important, as these are areas where commercial interest is limited.

Despite these challenges, research on diagnostic tools and biomarkers remains a focus of AD research. Scientists are investigating the value of different types of markers, including those found in CSF, through imaging, and in plasma, which are outlined in the following sections.

**Cerebrospinal fluid (CSF) biomarkers:** Because CSF is in direct contact with the brain, its levels of beta-amyloid and tau protein are the most explored candidates for AD biomarkers, given their roles in the formation of the plaques and tangles characteristic of AD. Studies have found that AD patients have a higher tau protein level than normal subjects and that tau level is a good indicator of neurodegeneration. A lower CSF beta-amyloid level was observed in AD patients, with the drop occurring even before beta-amyloid could be detected in brain imaging. These two markers may be used to differentiate patients with AD from healthy individuals, but further efforts are needed to standardize the testing procedure and to understand whether they also can be used to determine disease stage. In addition to CSF beta-amyloid and tau, the level of beta-secretase, an enzyme involved in the production of beta-amyloid, has been identified as another potential marker.

**Imaging:** Imaging tools are an important area of diagnostic research, and variables tracked through imaging include brain volume, brain activities, and presence of specific proteins. Decrease in brain volume and enlargement of ventricles, driven by loss of neurons, are candidates as AD biomarkers. Changes in specific areas of the brain, such as the hippocampus, are studied for evidence of greater
decrease and sensitivity. Abnormalities in brain activities also are considered to be potential markers, including the measurement of cerebral metabolic rate for glucose through use of FDG PET,\textsuperscript{15} which can identify areas where neuron synaptic activity is abnormal; and hyperactivity in specific sites prior to loss of hippocampus function, detected through functional MRI. Finally, detection of specific proteins such as beta-amyloid is another area of research, using imaging agents such as the Pittsburgh Compound B (PiB), a PET imaging agent that binds to beta-amyloid plaques. In addition, new imaging technology is emerging, enabling imaging of inflammation, other proteins such as tau and alpha-synuclein, or mitochondria function.

**Plasma biomarkers:** Because biomarkers based on blood samples are more accessible than those based on CSF, they are currently the focus of research. Beta-amyloid level in plasma is being studied as a predictor of AD risk. In addition, a test of a panel of plasma proteins was identified to be associated with neuron death in the hippocampus.

---

**Alzheimer's Disease Neuroimaging Initiative (ADNI)**

ADNI, launched in 2004, is a five-year effort studying 200 elderly controls, 400 subjects with MCI, and 200 with Alzheimer's disease to identify the biomarkers of AD and MCI. Its $67 million budget is funded by the National Institute of Biomedical Imaging and Bioengineering and the National Institute on Aging, as well as a consortium of pharmaceutical companies and nonprofit organizations. The study takes an integrated approach, combining MRI, PET, blood tests, and CSF analyses. Researchers hope to clearly identify a metric, or combination of metrics, that can serve as a biomarker for different purposes, such as early diagnosis, disease progression, and treatment effectiveness. As the project nears its end, research results are just starting to be published.

A key characteristic of ADNI is its collaborative nature. It has more than 50 participant sites involving a large number of investigators, and industry funders participate in the project as members of the Industry Scientific Advisory Board. ADNI is now being replicated in other parts of the world, including Australia, Europe, and Japan. In addition, DIAN (Dominantly Inherited Alzheimer Network), which focuses on profiling familial AD, also is using protocols developed by ADNI, as are ADNI-like studies in Japan and Australia. These efforts are not only meaningful in finding an AD marker but they also are generating a large dataset based on the same collection methodology, which is highly valuable for further research.

ADNI is a unique opportunity to observe a large number of patients, and the research community seeks to actively leverage the opportunity. For example, collection of postmortem brain samples and genetic data were added to the project as additional funding was secured, which enables researchers to take into account the extent of pathological features in the brain and the impact of genetic risk factors in conducting biomarker research.

The AD research community is planning for an extension of ADNI (ADNI II), to enable additional data collection and analysis, building on the efforts of the past five years. Individual contributions to ADNI can be made through the Foundation for the NIH.

---

\textsuperscript{15} FluroDeoxyGlucose Positron Emission Tomography, a PET scan using an imaging agent to assess glucose metabolism.
Current treatment options can delay the progression of symptoms by a few months, but the dominant scientific hypotheses on the genesis of AD suggest that existing treatments may not address the root cause of the disease. As a result, the development of disease-modifying treatment is one of the most important goals of AD research and also the most significant challenge.

Much of the treatment development efforts have focused on targets based on the major hypotheses of AD—beta-amyloid, and to a lesser extent, tau protein. However, more diverse targets should be explored. Although beta-amyloid plaques and tau tangles are the hallmarks of the disease, it is yet to be confirmed whether they are the most appropriate targets for therapy. Results from a recent trial of an agent targeting the mitochondria illustrated the need to diversify targets and experiment with different approaches.

While a disease-modifying treatment is the holy grail of the AD community, symptomatic treatment should not be ignored. This is especially important because unless disease-modifying treatments are applied in the early stage of the disease, loss of cognitive function will still occur. Symptomatic treatments, both drugs and non-pharmaceutical approaches, will remain relevant as they address the needs of later-stage patients and help reduce the caregivers’ burden.

In addition to the need for diversified treatment strategies, new approaches for developing therapies are required. Most of the current treatment research efforts are based on specific hypotheses and focus on affecting a specific pathway. Yet, how each intervention affects not only the targeted pathway but also other variables is not well studied. Therapeutic approaches aimed at multiple targets, based on systemic perspectives, have not been adequately explored. Leveraging systems biology, bioinformatics, modeling capabilities, and in silico models will encourage development of systemic strategies.

The need for an integrated approach does not stop with individual studies of AD. Interdisciplinary approaches across diseases are needed, especially because AD shares many features with other neurodegenerative diseases such as frontotemporal dementia, Parkinson’s disease (PD), tauopathies, and amyotrophic lateral sclerosis (ALS). This is becoming increasingly important as research suggests that treatment of patients with clinical disease may need to focus on further downstream targets, which may be common to other neurodegenerative diseases. Also, a comprehensive study is needed, similar to ADNI, combining biomarkers and therapeutic strategies for prevention and treatment. In addition, more research is needed on “repurposing” off-patent drugs that have been developed for other indications but have the ability to manipulate AD targets.

Finally, the clinical trials process poses another challenge to treatment development. The process is very slow, and adequate quality control is difficult. In addition, ambiguity surrounding FDA’s drug approval process and the need for large, well-controlled trials pose significant challenges for the development of effective treatments for AD.
approval standard is a challenge. FDA requires that trials demonstrate disease modification by including a late-start group in the trial and showing that patients who started the treatment in later disease stages do not demonstrate the same response as those who started earlier treatment. However, designing such trials and measuring their impact is difficult to achieve in Phase 2, as these studies are meant to rely on smaller study groups over a shorter period of time. As a result, the field is facing difficulties generating clear efficacy signals in Phase 2. Some trials have opted to rely on signals in biomarkers still in development, while others choose to conduct larger and longer trials—which entail significant increases in cost and human risks. Using biomarkers to augment the power of trials can solve part of this problem and reduce required sample size. Outcomes from the ADNI study already are suggesting that this is possible. Furthermore, the fact that current treatment strategies focus on novel pathways adds additional regulatory uncertainties. ACT-AD (Accelerate Cure/Treatment for Alzheimer’s Disease), a coalition of organizations seeking to accelerate the developments of treatment for AD, provides an avenue through which issues with the regulatory environment are raised and dialogues with appropriate authorities are initiated.

The following sections outline the current areas of focus in treatment research.

**Strategies targeting beta-amyloid**: Treatment research focusing on beta-amyloid has received the most investment of the disease-modifying strategies. Strategies targeting beta-amyloid include:

- Reducing beta-amyloid production
- Increasing beta-amyloid removal
- Preventing aggregation of beta-amyloid

A key strategy targeting the beta-amyloid pathway is to reduce the production of beta-amyloid in the brain. The enzymes involved in the production of beta-amyloid—beta and gamma secretases—are the targets of drug development, with multiple compounds in various stages of preclinical and clinical development. Strategies include directly targeting an enzyme, enhancing proteins that reduce the enzyme’s action, targeting the enzyme’s action site on APP, or changing the cellular environment to reduce enzyme activity. Scientists also are investigating the other roles that these enzymes play, in search of ways to reduce beta-amyloid creation without affecting other functions. Investigation has begun on therapeutics that address both targets at a moderate level, an effort to minimize the side effects of fully suppressing one of the two enzymes, given their multiple functions. Additionally, scientists are researching compounds that can increase alpha secretase, which also processes APP in a way that prevents the production of the toxic variety of beta-amyloid.

**Increasing the removal of beta-amyloid** is another potential treatment strategy, and immunotherapy has been at the center of this approach. Active vaccination and passive immunization, injecting antibodies to the patients to bypass potential adverse side effects, are both being explored in animal and clinical studies using different technologies and antibodies. Other efforts in earlier stages of development are focused on increasing immune reaction against beta-amyloid including intravenous immunoglobulin—which contains pooled antibodies and is often used to treat immune deficiencies and autoimmune disease—oral vaccines, DNA vaccines, T-cell transfers, and encapsulation of beta-amyloid. In addition, strategies to boost the body's ability to break down beta-amyloid peptides through enzymes are also in exploration, although still in early stages.
Another strategy targeting beta-amyloid focuses on a further downstream event, the aggregation of beta-amyloid, which gives the protein its damaging properties. Such aggregation requires a metal ion as a core, so those metals are a target for drug development. PBT2, which targets this mechanism, has recently been tested in a Phase 2 trial, demonstrating expected changes in CSF markers when administered at high doses. In addition, the activities of some gamma secretase modulators also interfere with the aggregation process of beta-amyloid, in addition to reducing its production.

Reduction of abnormal tau protein: Clearing abnormal tau protein from the brain is one treatment approach. Some enzymes appear to have the potential to break down tau tangles, and immunotherapy against tau showed cognitive improvement in animal models. Another strategy is to reduce the development of abnormal tau protein. Lithium, a bipolar disorder drug, may be able to normalize tau protein balance by inhibiting an enzyme needed in phosphorylation of tau, and early clinical research is ongoing. Further downstream, scientists are screening compounds for their ability to prevent tau aggregation. One such compound is currently being tested in clinical studies, although the long-term benefit and efficacy still need to be demonstrated. Another example is polyphenol, an antioxidant present in grapes, which showed beneficial effects in animal studies. Grape seed extracts also have shown potential to reduce beta-amyloid and inflammation in animal models.

Mitochondria enhancers: While the role of mitochondria in AD's progression is yet to be fully understood, Dimebon, a compound suggested as enhancing mitochondrial function, has shown efficacy in recent trials. Indeed, it is the only treatment that has shown significant clinical effect in a Phase 3 trial, and now is in its second pivotal Phase 3 trial. The distribution and activity of mitochondria are affected in AD and are believed to impact neurodegeneration, though details on how this compound actually works need to be further clarified. Given its positive impact in clinical trials, the compound and research on its mechanism of action are becoming more important.

Secondary symptom management: Management of the secondary symptoms of AD, such as psychiatric symptoms, is another area of research. Studies have been conducted to understand how different AD drugs affect secondary symptoms. Research is focusing on the effect of antidepressants on cognitive capability and on the safety and effectiveness of atypical antipsychotic drugs in managing symptoms. One recent trial indicated that the use of such medications leads to an increase in mortality. Non-drug intervention strategies also are in development, including bright light therapy, aromatherapy, exercise, behavioral strategies, training, and specialist inputs.

Other: In addition to the aforementioned treatment development efforts, various other treatment strategies are being explored, including treatment strategies focused on lowering cholesterol. High cholesterol is suggested to be a risk factor for AD and a study has associated ApoE4 gene carriers with high cholesterol. Some research has suggested that statins, used to treat high cholesterol, are able to reduce the level of beta-amyloid; however, results from different efforts have varied so far and data are not yet conclusive. In addition, agents that seek to improve the activities of neurotransmitters and their receptors in the brain, working similarly to existing AD drugs, are in clinical trials, although the effects are yet to be clearly demonstrated. Other treatment strategies pursued include those focusing on neuroprotective peptides to reduce the impact of toxic tau, anti-
inflammatory agents, and signaling molecules to reduce inflammation, which are in clinical trials. Approaches in even earlier stages of development include strategies to protect neurons against the toxic effects of ion imbalance and strategies to encourage the generation of new neurons.

In addition to therapies based on drugs and biologics, interventions based on training and diet also are in development. Examples include cognitive training, home-based physical activities, stimulation exercises, and medical food.\textsuperscript{16}

**Care Delivery**

<table>
<thead>
<tr>
<th>Key areas of research:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology enhancement for caregiving</td>
</tr>
<tr>
<td>Caregiver counseling and support</td>
</tr>
<tr>
<td>Integrated care provision</td>
</tr>
</tbody>
</table>

Given the complex nature of AD, finding ways to improve the delivery of care to AD patients and to provide consistent, ongoing support for their caregivers is important. In addition, there is a need for additional research on better care delivery, including better training of clinicians and research on nursing care. Patterns of care interaction are suggested to affect clinical outcomes in other diseases. The following section outlines major research in care and delivery.

**Technology enhancement for caregiving:** Scientists are developing strategies to reduce the burden placed on caregivers, e.g., the need to travel to the doctor's office, by studying the feasibility of examining patients in their homes using telemedicine. Assistive technology, such as tools that provide reminders, detect negative events such as falls, and track the patient through GPS, also are in development to assist caregivers and maintain patient independence.

**Impact of caregiver counseling and support:** Many caregivers prefer to care for an AD patient at home. Home care also delays the need for a managed care facility, which reduces the overall cost of AD. Researchers are testing different strategies to reduce caregiver stress and improve their health and quality of life, including intensive counseling and education for caregivers and online support groups. Studies are also underway to better understand how caregivers' psychological burdens differ across cultures, and how the pattern of interaction with caregivers affects a patient's resistance to or acceptance of care.

**Integrated care provision:** Alternatives to the current care arrangement, where the primary care physician is solely in charge of care for dementia, are being explored. Researchers are investigating a model of a collaborative team in which a care manager—an advanced practice nurse—works with the primary care physician with the support of a geriatrician, a geriatric psychiatrist, and a psychologist. Results indicate improvement in neurological tests and psychiatric symptoms. Another study emphasizing collaboration across healthcare agencies also has yielded positive effects, without increasing healthcare usage. Other efforts to develop coordinated care models are ongoing.

\textsuperscript{16} FDA states "A medical food is prescribed by a physician when a patient has special nutrient needs in order to manage a disease or health condition, and the patient is under the physician's ongoing care."
## Research Infrastructure

### Summary
Table 5 summarizes the major tools available for AD research and areas where more investment is required to overcome challenges and accelerate research. Major tools and associated challenges were identified and prioritized through consultation with FasterCures’ PAS Scientific Advisory Board for AD.

<table>
<thead>
<tr>
<th>Tool category</th>
<th>Existing tools and efforts</th>
<th>Challenges or areas requiring investment</th>
</tr>
</thead>
</table>
| Biospecimens          | • Alzheimer’s Disease Centers collect biospecimens  
  • The National Cell Repository collects DNA samples for late-onset AD  
  • Additional biospecimens collected through large longitudinal studies, including Alzheimer’s Disease Neuroimaging Initiative and Dominantly Inherited Alzheimer’s Network | • Tissue and brain samples linked with clinical data are not consistently collected despite their importance to basic research  
  • Limited specimen and clinical data available for healthy controls, which makes it difficult to draw comparisons with patient samples                                                                                                                                 |
| Animal models         | • Multiple mouse models based on genetic mutations of early-onset AD and tauopathies that mimic the symptoms of the human form of AD, as well as rat and fly models  
  • Primate models with spontaneous disease, but with limited use due to time and cost constraints as well as ethical issues | • Limited predictive value of transgenic animal models due to differences with the human form of the disease  
  • Difficulties in comparing experimental results due to the proliferation of multiple models, limited availability, and lack of standard procedures                                                                                                                                 |
| Research training     | • Development of the next generation of researchers through traditional academic programs (e.g., M.D., Ph.D. or joint programs)                                                                                           | • Lack of people with translational research and drug development expertise outside of industry and limited training opportunities                                                                                                                                 |
| Drug development platform | • The National Institutes of Health, Harvard, and industry provide facilities to conduct drug development research                                                                                                      | • Limited drug development infrastructure outside of industry                                                                                                                                                                                                 |
| Clinical trials       | • Most trials are conducted as industry-led efforts  
  • The Alzheimer’s Disease Cooperative Study is a trial network with over 90 sites  
  • The Dominantly Inherited Alzheimer Network will be developed as a patient registry of early-onset AD | • Enrollment limited as care practice is led by primary care physicians and burden to caregivers is high, despite the large patient pool  
  • Quality of trial results not consistent                                                                                                                                                                                                 |
| Data standards        | • Alzheimer’s Disease Centers are required to collect patient data according to National Institute of Aging (NIA)-defined uniform data set  
  • NIA Genetics of Alzheimer’s Disease Data | • Standards are needed for sharing clinical and research data and pooling them to draw new insights                                                                                                                                                      |
NIH has played an instrumental role in establishing infrastructure required for AD research. NIA, the lead agency on AD within the NIH, has been funding 29 Alzheimer’s Disease Centers (ADC) across the country since 1984 to facilitate research, education, and treatment of AD, and their activities and data collection are coordinated by the National Alzheimer’s Coordinating Center (NACC), created in 1999.

**Biospecimens**

Biospecimens are an important tool for basic research, especially when collected using a consistent methodology and linked to clinical data. In AD research, NACC serves as a clearinghouse for biological specimens collected at ADCs. Researchers can identify the ADC where specific samples are located through NACC, and then apply to the individual ADC for sample access for their own studies. Biospecimens obtainable through this mechanism include brain tissues, CSF samples, DNA, and serum samples. In total, ADCs have banked 20,800 brain tissue samples, 2,800 CSF samples, 3,500 DNA samples, and 1,300 serum samples. About two-thirds of the samples are from AD patients, less than five percent from normal controls, and the remaining from patients with other dementia and related diseases. However, the biospecimens and associated data may not be representative of the demographic diversity of the entire patient population, which limits the robustness of the analyses.

The National Cell Repository for Alzheimer’s Disease, another program initiated by NIA, collects genetic data on late-onset AD from 1,000 families with members affected by the disease. The repository aims to make DNA samples and cell lines available to the research community, to enable genetic and risk factor research. The repository also includes information on family history, demographics, medical records, and biopsy findings.

ADNI and DIAN studies, both structured as longitudinal observational studies, collect CSF and blood serum. Specimens collected through ADNI are made available to the research community after approval by the Research Allocation Review Committee. As for DIAN, its protocol and access processes are yet to be published; however, its data collection protocol is required to be in line with ADNI's to ensure compatibility.
With several multiple large-scale biospecimens collection efforts, the AD research field is not facing the challenge of limited availability of tissue samples. However, there is a critical lack of samples linked with sufficient clinical data, which would enable scientists to correlate molecular and biological data with clinical manifestations of the disease. Another challenge is limited availability of samples and associated clinical data from normal controls. Many ADCs are reaching out to pathologists in areas other than neurodegenerative diseases to acquire control specimens.

**Animal Models**

Animal models are the key media through which potential treatment targets and methods are first identified and then studied. However, animals do not develop the same disease as humans. In some cases, animal models are based on a similar disease that animals contract, and in other cases, scientists artificially induce the disease to create animal models of disease.

Most of the AD disease models are artificially developed, especially by manipulating genes to replicate the symptoms of disease, since animals do not usually spontaneously develop AD. Such methods have led to multiple animal models, including the mouse, rat, and fruit fly. One of the most recent accomplishments in animal models was the development of the triple transgenic mouse, which exhibits both hallmarks of AD, beta-amyloid plaques and tau tangles. The Alzheimer Research Forum (Alzforum) maintains a list of disease mouse models based on gene mutation, along with the contact information for acquisition. Many transgenic mice are available from the Jackson Laboratory, which breeds and distributes mouse models for multiple diseases.

To date, genetic mutations known to cause AD in humans are associated with early-onset familial AD, rather than late-onset AD, which accounts for a majority of cases. Mutations that cause early-onset familial AD generally increase the production of beta-amyloid; however, these mutations are not observed in the late-onset form of the disease. As a result, although animal models of AD develop the plaques and tangles characteristic of the disease, the underlying mechanism may not correspond to the late-onset disease. This limits the predictive value of existing animal models, as there is uncertainty as to whether research results from animal models will also apply to human patients. Alternative models are needed. Some studies focus on primates, which can develop AD pathology spontaneously, but their use is not as widespread because of the relatively long lifespan of primates, the cost of such research, and animal welfare concerns.

In addition to scientific limitations, the practice through which models are developed and shared limits their potential. Often, animal models are treated as proprietary, limiting access for researchers, and this has resulted in the development and use of competing disease models. This, combined with lack of standardized operating procedures (e.g., age or number of trials), has made it difficult to compare experimental results, assess targets, compare multiple targets, and predict the validity of a target. An open source approach to research tools and a standardized practice guideline on target validation are required to more rapidly move the field forward.

**Research Training**

With the high interest in treatment development, academia’s attention to translational research in drug development is increasing. While there have been significant efforts to increase the pool of
researchers with expertise in both basic and clinical research, efforts to build a cadre of researchers in academia with translational research expertise have been lagging, and adequate opportunities for such training have not been in place. As a result, leaders in academia point out that there is a need for building multidisciplinary translational research expertise. Such efforts will require the participation of the pharmaceutical industry, where the relevant expertise currently resides.

**Drug Development Platform**

Another barrier to drug development outside the pharmaceutical industry is the lack of infrastructure with adequate technological support and resources. While there are a few institutions focusing on drug development, including the NIH Chemical Genomics Center and the Harvard NeuroDiscovery Center, capacity is limited. Investing in such infrastructure may become more important, with the trend of decreasing venture capital funding for early-stage drug development, which adds pressure on the academic and nonprofit sector to focus on this area.

**Clinical Trials**

Clinical trials are a crucial step in treatment development, requiring large financial investments, typically made by industry. In addition to the quality control issues mentioned in the Treatment Research section, patient enrollment is a major obstacle to clinical trials. Resources such as clinical trial networks and patient registries can accelerate recruitment by organizing patients and data.

In 1991, NIA and the University of California San Diego created the Alzheimer’s Disease Cooperative Study (ADCS), which conducts multi-site trials that are not attractive to industry. These include trials for compounds without patent, those already in the market for other indications, or new compounds from non-industry sources. ADCS includes a data center, an administrative center, and 93 clinical sites across North America (88 in the United States and 5 in Canada).\(^{17}\) To date, it has launched 21 trials, out of which 18 were for drug compounds and 3 for development of tools such as clinical cognitive tests.

DIAN, also funded by NIA, was initiated in summer 2008. It is an effort to study the process of disease onset and progression in the early-onset familial form of AD, in which the more predictable onset enables better research design. The study will enroll families with early onset AD in the United States and internationally, and create a registry of families with early-onset familial AD.

With a clinical trials network infrastructure in place, a more important problem in conducting trials is low enrollment, despite AD’s large population burden. Early-stage patients often are asymptomatic, so it is difficult to identify candidates for early-stage studies. In addition, primary care physicians, in charge of most of the patient care, are not always familiar with or knowledgeable about available trials. The demands of clinical trial participation also may be more than caregivers can handle, when coupled with everyday responsibilities. To increase recruitment and enrollment, marketing and education efforts must target patients and caregivers, primary care physicians must be engaged in the clinical trials process, and technology should be leveraged to reduce caregiver  

\(^{17}\) Not all sites may participate in every trial.
Recent research points to travel inconvenience as a major factor discouraging trial participation, and solving the issue with home visits was suggested to increase participation. Researchers also are exploring the option of conducting trials overseas to increase enrollment.

**Data Standards**

NACC requires that ADCs collect patient data according to specific standards. Initially, the centers were required to collect a minimum data set, which includes brief demographic and clinical data. In the early 2000s, however, NIA formed the ADC Clinical Task Force to define the new data set and standard protocol. In 2005, the uniform data set was rolled out, to include standardized clinical testing, diagnostics, and other clinical data. Unlike the minimum data set, the uniform data set was designed to be collected over time based on a standardized protocol to create consistent longitudinal data. In addition, each center collects neuropathology data, which describe the features of ADC patients biopsied after death. These data are available through the NACC Web site, with different access levels based on each project.

In addition, NIA requires that all genetic data on late-onset AD derived from NIA-funded projects be deposited at the NIA Genetics of Alzheimer’s Disease Data Storage Site (NIAGADS) or other approved sites. Unlike the National Cell Repository for Alzheimer’s Disease, which collects raw DNA samples, NIAGADS collects processed data ready for analyses, such as genotype data and genetic maps. In addition, NIAGADS collects data on family history, demographic information, and dementia status, along with genotype. Researchers apply directly to NIAGADS to access data. NIA also is launching a genome-wide association study, which will be able to confirm newly suggested genetic risk factors and identify more.

ADNI and DIAN studies also contribute to establishing data standards and distributing data to researchers. Significant imaging data, including MRI and PET scans, are generated from ADNI based on uniform protocols and are made available to the research community. DIAN is likely to provide similar arrangements.

**Communication**

In addition to knowledge sharing through journal publications and scientific meetings, Alzforum is another tool through which knowledge sharing occurs in AD research. Alzforum started as a gateway to publications on AD targeting AD researchers, with a professional editorial function. Over time, it has grown into a virtual community, where comments on papers are shared and even some pre-publication results are discussed in virtual chats. In addition, it hosts continuously updated databases such as AlzGene, which create meta-analyses of genetic association studies on AD and disseminate the aggregate results as they are computed. Approximately 30 to 50 percent of all active AD researchers are estimated to be members of the site.
Clinical Trials

As of February 2009, there were 264 ongoing clinical trials for AD. AD has a slightly higher share of trials in Phase 1 than other diseases (Figure 9).

In terms of sponsors, investment by commercial players was especially strong, with industry supporting over 50 percent of all trials. Involvement of NIH and other government agencies was on par with other diseases. Because of significant industry sponsorship, the proportion of support from other players such as universities and nonprofit organizations was smaller than for other diseases.

Thirty seven trials were observational, focusing on better understanding of normal aging or natural disease progress, while the rest were interventional trials focusing on modifying the disease outcome. Over 60 percent of AD trials involved a drug or a biologic, and 14 percent were focused on behavioral intervention. Other trials include studies involving radiation and combinations of different types of interventions. This category had a lower share of trials compared to other diseases.

For all types of trial sponsors, those involving drugs or biologics accounted for the largest shares, consistent with the aggregate share. The share of drugs and biologics was especially high for the trials sponsored by industry, amounting to 95 percent of all industry-sponsored trials. In comparison, 62 percent of NIH’s trial portfolio and 49 percent of trials by other

---

18 Trials with multiple types of sponsors are accounted for in each sponsor type, but this is a penetration measure, while the phase distribution is a share of total.
funders were drug trials, with a larger share of trials focusing on behavioral treatments, procedures, and observational trials.

**Funding**

NIH’s investment in AD research totalled $645 million in 2007, only a marginal increase over 2006, and actually lower than annual investments made in 2004 and 2005 (Figure 10). In addition, the share of NIH’s funding for AD as a share of total NIH budget has steadily decreased over the last five years. Going forward, estimates for NIH’s AD research budget in 2008 and 2009 remain stagnant, even without accounting for inflation, although the economic stimulus package may result in increase in funding available for AD research.

The overall decreasing trend of NIH’s spending on AD research coincides with a period of marginal increase in NIH’s overall budget, which grew at a 1.8 percent compound annual growth rate during 2003-2007, unadjusted for inflation.

In addition to traditional NIH grants, NIA also has in place its Translational Initiative. Launched in 2004, this initiative provides grants to accelerate the drug discovery process by funding the research needed for FDA’s Investigational New Drug (IND) approval. It also supports pilot studies on promising compounds and non-drug interventions. At the same time, however, a stagnating budget, combined with large projects such as ADNI and genome-wide association studies, limits the available funds for new projects.

With over 5 million AD patients in the United States, the current level of NIH’s investment translates into $122 of research investment per existing patient. The Alzheimer’s Association estimates the cost of Medicare alone for an average AD patient amounts to $13,000, over 100 times that of the research investment.

---

19 In January 2009, NIH updated the methodology through which it calculates the investment in each disease. Based on this new methodology, the investment in AD amounted to $411 million in 2007 and $412 million in 2008. However, in order to show the trend over an extended period of time, this report shows the data based on the historical methodology.
Market Analysis

Overview

Five treatment options currently are available for AD in the United States: Aricept by Eisai and Pfizer, Namenda by Forest Laboratories, Razadyne by Janssen (part of Johnson & Johnson [J&J]), Exelon by Novartis, and Cognex by Sciele (in order of revenue size in the United States). While these medications can alleviate symptoms and delay disease progression, they do not address the disease mechanisms that scientists believe are the underlying causes of AD. This unmet medical need, combined with the expected increase in the patient pool, is drawing commercial interest in the disease. There are currently 74 drugs in clinical development for AD. Among these, 31 are in Phase 1, 35 in Phase 2, and 8 in Phase 3. In addition to companies that draw a large share of their revenues from AD treatments, many companies without an AD drug in their portfolios have efforts underway to develop AD drugs, including Merck & Co, Pfizer, and Roche.

Products

Among the five treatment options for AD in the United States (Table 4), Donepezil is the only drug approved to treat all three stages (mild, moderate, and severe) of AD; memantine is approved for the moderate and severe stages, and the rest for the mild and moderate stages.

The active ingredients used in AD drugs can be characterized by their mechanisms of intervention:

- Reduce neurotransmitter decomposition: Donepezil, Galantamine, Rivastigmine, Tacrine
- Reduce excitotoxicity: Memantine

While these drugs delay the progress of clinical symptoms by a few months, they do not target beta-amyloid or tau protein, which are considered the root causes of the disease.

Cognex was approved in September 1993 as the first drug for AD. The drug was originally developed by Warner-Lambert, but Pfizer, with which Warner-Lambert merged in 2000, sold the marketing rights to Sciele. For the most part, Cognex has been replaced by other drugs because of side effects, inconvenience, and poor absorption. The future availability of Cognex is uncertain; Sciele’s contract with the supplier of the active ingredient expires in 2008.

Table 4: Companies with AD Drugs Launched in the U.S.

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Brand Name</th>
<th>Company</th>
<th>Patent Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Aricept</td>
<td>Eisai / Pfizer</td>
<td>2010</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Razadyne</td>
<td>J&amp;J (Janssen)</td>
<td>2008</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Exelon</td>
<td>Novartis</td>
<td>2012</td>
</tr>
<tr>
<td>Tacrine</td>
<td>Cognex</td>
<td>Sciele</td>
<td>2008-2013</td>
</tr>
<tr>
<td>Memantine</td>
<td>Namenda</td>
<td>Forest</td>
<td>2010-2013</td>
</tr>
</tbody>
</table>

Sources: SEC filings, Drugs@FDA, FasterCures analysis.
The second AD drug to enter the U.S. market was Aricept. Approved in 1996, Aricept was developed by Eisai and uses a similar mechanism as Cognex. Eisai co-markets Aricept with Pfizer in the United States, because it initially lacked marketing capability. Aricept’s sales in the United States are over $1 billion; approximately 90 percent of its sales in the United States are now through Eisai.

Exelon, developed by Novartis, was approved for AD in 2000, and for dementia associated with Parkinson’s disease in 2005. A patch formulation designed to enhance patient convenience was recently introduced.

Razadyne was the most recent AD drug to enter the market based on the same treatment hypothesis as the aforementioned drugs. It was originally named Reminyl, but its name in the United States was changed to Razadyne to avoid confusion with the diabetes drug Amaryl. Razadyne is marketed by Janssen Pharmaceutica and Ortho-McNeil Neurologics in the United States, which are both part of J&J.

Namenda entered the AD market in 2003. It is a different type of AD drug, focusing on reducing neuron death caused by excitotoxicity. It was originally developed by German-based Merz; Forest Laboratories markets it in the United States.

**Market Share**

In recent years, the overall AD drug market in the United States has been growing at 25 percent per year; its market is now close to $3 billion (Figure 11). Globally, the AD drug market is estimated to be as large as $4.1 billion as of 2005 and is expected to reach $5.7 billion by 2010, according to the market research firm Wood Mackenzie, as quoted by *Nature Medicine*.

The U.S. market has been largely dominated by Aricept. The use of Namenda, the first drug to be approved for severe AD, has been growing rapidly, at 36 percent per year. Aricept was also approved for severe AD in 2006, and these two drugs are often used together.

---

Enhancing convenience for patients has been the key area of improvement for existing drugs. Versions that can be taken less frequently, as a liquid rather than a tablet, or as a transdermal patch rather than an oral medication, have been introduced, or are in development, to meet the needs of aging patients.

Generic competition has just begun to enter the AD drug market, and FDA granted approvals to several generic producers. It is estimated that generic and new drugs may reduce the share of cholinesterase inhibitors to 31 percent of the total market by 2015.

### Pipeline

Currently, there are 74 drugs under development for AD, including medical food and symptomatic treatments. Figure 12 shows the distribution of the development efforts across the research pipeline. Out of the total, 42 percent are in Phase 1 trials and 45 percent in Phase 2 trials. There are 10 compounds in Phase 3 trials, so new drugs may enter the market in the next few years.

There are about 45 players involved in the development of AD drugs. There are six commercial players that have three or more AD drug candidates in their pipelines (Table 5).

Other companies with a Phase 3 candidate in the pipeline include: 21

- Forest Laboratories (1)
- Ipsen (1)
- Martek Biosciences (1)
- Medivation22 (1)
- Somerset (1)

---

21 Neurochem’s Alzhemed, which prevents beta-amyloid plaque formation, is another compound that advanced to Phase 3, receiving much media attention. Phase 3 trials were completed in North America and Europe in mid-2007. However, the company decided to pursue the compound as a nutraceutical rather than a pharmaceutical agent because of the limited impact demonstrated. Myriad’s Flurizan, targeting gamma secretase, also advanced to Phase 3 but failed to reach its endpoint.

22 This compound, Dimebon, has a co-development agreement with Pfizer. This is not included in Pfizer’s pipeline on Table 5.
Table 5: Commercial Players with Three or More AD Drugs in the Pipeline, 2008

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer/Wyeth</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Roche/Genentech/Memory</td>
<td>5</td>
<td>3</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Merck</td>
<td>3</td>
<td>3</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td></td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Elan</td>
<td>2</td>
<td>1</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

*Source: PhRMA.*
Commercial Players

Overview

This section provides a brief summary of selected companies active in AD disease R&D. Companies surveyed either are involved in sales of the five approved AD drugs (Figure 13), in order of the importance of AD drugs for the company, or have five or more AD drug candidates in their R&D pipelines (Table 5). For each company, a brief discussion includes its existing and potential drugs, sales, and R&D strategy for AD.

While not discussed separately because they do not have a large portfolio of compounds relevant to AD, several additional companies are developing therapeutics. Those receiving media attention include Baxter Bioscience with an intravenous immunoglobulin in Phase 2 trials; Medivation with Dimebon, a treatment believed to enhance mitochondrial activity moving to Phase 3 trials; Prana Biotechnology with PBT2, a compound that reduces the availability of metal that acts as a core for beta-amyloid aggregation in Phase 2 trials; and TauRx Therapeutics with Rember, a tau aggregation inhibitor that completed a Phase 2 trial.

Key Companies

Eisai

Eisai, headquartered in Japan, derived $2.5 billion in revenue from Aricept in 2007, with approximately two-thirds of this total derived from the U.S. market. Its AD revenue is the largest of all players with an AD drug in their sales portfolios. Aricept accounted for 40 percent of Eisai’s total revenue. Its two major drugs, Aricept and AcipHex/Pariet, a treatment for acid reflux, accounted for approximately two-thirds of its total revenue.

23 Sciele Pharma is excluded from this review because it has limited focus on AD and has recently been acquired by another company, Shionogi & Co., based in Japan. Wyeth is not reviewed either, since it has been acquired by Pfizer.
In 2007, Eisai spent $1.2 billion—19 percent of its total revenues—on R&D. Eisai’s R&D efforts are focused on neuroscience, oncology, and vascular and immunologic diseases. Areas of research within neurology include epilepsy, depression, pain, multiple sclerosis, and AD. Research efforts on AD are mostly based on Aricept—enhancing formulations and expanding indications for which the drug can be used.24

**Forest Laboratories**

New York-based Forest Laboratories, reported $830 million in sales of Namenda in 2007, which equaled 24 percent of its revenue. Forest’s sales of Namenda are limited to the U.S. market, as the drug is marketed by other companies in the rest of the world. Lexapro, used to treat depression, accounted for 66 percent of Forest’s 2006 sales. Other medications in Forest’s portfolio relate to hypertension, anxiety, and alcohol abstinence.

In 2007, Forest spent $671 million—19 percent of its revenue—on R&D. A key component of Forest’s R&D strategy is to license in promising products in development from other companies, pulling together the partner’s intellectual property and Forest’s capability in the drug development process. For example, Forest in-licensed the rights to market Namenda in the United States from the German company Merz; Lexapro was developed by Lundbeck, which also markets Namenda in other parts of the world. Forest’s current pipeline includes drugs for asthma, cardiovascular diseases, stroke, AD, neuropathic pain, fibromyalgia, infectious diseases, and central nervous system disorders. It is developing an enhanced formulation of memantine with Merz.

**Merz**

Merz is a family-owned company based in Germany, focusing on diseases of the central nervous system, dermatology, specialty pharmaceuticals, and consumer health.25 It developed memantine, which is marketed as Namenda by Forest Laboratories in the United States, Ebixa by Lundbeck, and Axura/Akatinol by Merz in the rest of the world. In 2007 Merz recorded sales of $166 million for the drug, amounting to 18 percent of total revenue.

In 2007, Merz spent $128 million, or 14 percent of its total revenue in R&D, with neurology and aesthetic dermatology being its major areas of focus. AD efforts include improving the formulation of memantine and a compound about to enter clinical trials.

**Lundbeck**

Based in Denmark, Lundbeck distributes memantine under the brand name Ebixa in selected markets outside of the United States and Japan through an in-licensing agreement with Merz. Its key products include Ebixa (AD, accounting for 15 percent of its total revenue) and Cipralex/Lexapro (depression, 62 percent).

Lundbeck invested $402 million—20 percent of its revenue—in R&D in 2007. Its R&D focuses on mood disorders, psychoses, neurodegenerative disorders, epilepsy, sleep disorders, and stroke.

---

24 Numbers for Eisai do not include expenses incurred from mergers.

25 As such, publicly available data on the company are limited.
**Novartis**

Novartis, based in Switzerland, manufactures Exelon. Novartis in-licensed the patent for Exelon’s compound, which was originally granted to Proterra, AG, another Swiss company. For 2007, revenue from Exelon amounted to $536 million, or 1 percent of total revenue; about half of this revenue was earned in the United States.\(^{26}\)

Novartis spent $7.2 billion on R&D in 2007. AD is part of the company’s neuroscience portfolio, one of its top ten areas of research. Novartis has one AD drug candidate in clinical trials, a beta-amyloid immunotherapy agent developed in collaboration with Cytos Biotechnology in Switzerland.

**Pfizer/Wyeth**

Pfizer, based in New York, co-markets Aricept with Eisai. Pfizer derived $401 million in revenue, or one percent of total revenue, from Aricept in 2007.

Pfizer spent $8 billion, or 17 percent of total revenue, on R&D in 2007. Its R&D efforts are organized along 10 focus areas: cardiovascular, metabolic, and endocrine; neuroscience; inflammation; allergy and respiratory; infectious diseases; pain; oncology; urology and sexual health; gastrointestinal and hepatology; and ophthalmology. In September 2006, Pfizer formed an alliance with TransTech Pharma, which granted Pfizer exclusive worldwide rights to TransTech’s AD portfolio. Pfizer has four AD drug candidates in the pipeline, one in Phase 1, two in Phase 2, and one in Phase 3. The compound in Phase 1 is a gamma secretase inhibitor, and the Phase 2 candidates are a monoclonal antibody against a specific type of beta-amyloid and an oral agent against inflammation. The Phase 3 trials are for a medical food candidate. More recently, Pfizer has agreed to co-develop and co-market Dimebon, the mitochondria enhancer, with Medivation, which is in Phase 3 trials. In addition, it has also acquired Wyeth, which also has a significant AD pipeline, including bapineuzumab in Phase 3 trials in collaboration with Elan.

**Shire**

Shire, based in the United Kingdom, is a specialty pharmaceutical company focusing on attention deficit and hyperactivity disorder, human genetic therapies, and gastrointestinal and renal diseases. Its major products include Adderall, an attention-deficit drug, Pentasa, an ulcerative colitis drug, and Replagal, a treatment for Fabry disease. Reminyl—marketed as Razadyne in the United States and distributed by Shire in the United Kingdom and Ireland—accounts for one percent ($31 million) of its total revenue. The patent for Reminyl/Razadyne is owned by Synaptech, and Shire pays royalty to Synaptech in exchange for worldwide marketing rights. Outside of the United Kingdom and Ireland, Shire has in turn licensed the marketing rights to J&J.

Shire spent $567 million, or 23 percent of its revenue, on R&D in 2007. AD is not Shire’s focus area, and it has no AD drug candidate in the pipeline.

\(^{26}\) However, the importance of Exelon increased in 2008, as product revenue increased to $815M with launch of the patch formulation.
Johnson & Johnson (J&J)

J&J, based in New Jersey, is a diversified health company with a portfolio comprising pharmaceuticals, medical devices, and consumer health products. Ortho-McNeil Neurologics, formed by merging Ortho-McNeil Pharmaceutical and Janssen, is the entity in charge of marketing Razadyne worldwide (except in the United Kingdom and Ireland) and pays royalty to Shire, which in turn pays royalty to the original patent holder, Synaptech. J&J’s sales of Razadyne equaled $541 million in 2007, with a quarter sales made in the United States. Yet, Razadyne is not mentioned as one of the company’s top drugs since it accounts for less than one percent of its total revenue.

J&J spent $7.7 billion, or 12 percent of total revenue, on research in 2007. J&J Pharmaceutical Research & Development is the subsidiary in charge of R&D. AD, epilepsy, migraine, cognitive disorders, Parkinson’s disease and other movement disorders, stroke and neuroimmunology are the areas of focus within neurology.

Merck & Co.

Based in New Jersey, Merck & Co. is a pharmaceutical company with a diverse portfolio and revenue of $24 billion. Its business is organized into two categories: pharmaceuticals and vaccines. Key pharmaceutical products include Singulair for asthma, Cozaar/Hyzaar for hypertension and heart failure, Fosamax for osteoporosis, and Zocor for atherosclerosis.

In 2007, Merck invested $4.8 billion, or 20 percent of total revenue, in R&D. It has nine priority disease areas: AD, atherosclerosis, cardiovascular disease, diabetes, novel vaccines, obesity, oncology, pain, and sleep disorders. Merck has the largest AD pipeline of all companies, with six compounds in clinical stages. Compounds in Phase 1 trials include an active beta-amyloid vaccine and a gamma secretase inhibitor. Candidates in Phase 2 trials include a symptomatic drug and an agent that addresses inflammation. In 2006, Merck entered into collaboration agreements with the David Gladstone Institutes and Idera Pharmaceuticals, specifically mentioning AD as an area of cooperation. Merck also held a symposium in 2007 on AD and the blood-brain barrier to identify potential targets based on this biological mechanism.

Roche/Genentech/Memory

Based in Switzerland, Roche is comprised of both pharmaceutical and diagnostic businesses. For 2007, Roche reported revenues of $34.7 billion; cancer drugs accounted for 50 percent of the total, virology treatments for 13 percent, and drugs for inflammatory and autoimmune diseases for 8 percent, at par with treatments for metabolic and bone diseases.

Roche spent $7 billion, or 18 percent of total revenue, on R&D in 2007. It has five AD compounds in clinical development, including three collaborations with Memory Pharmaceuticals, two in Phase 1 and one in Phase 2. The other two AD drug candidates are in Phase 1. These include a compound targeting a specific type of receptor in the brain, in collaboration with Synosis, and a beta-amyloid antibody developed in collaboration with MorphoSys, a German company focused on the development of antibodies.
In 2008, Roche announced its acquisition of Memory Pharmaceutical, which had two compounds in development, one in Phase 1 and one in Phase 2, in addition to those in collaboration with Roche. All of Memory’s compounds were based on treatment strategies outside of beta-amyloid and tau.
Nonprofit Players

Overview

This section provides a brief overview of the nonprofit organizations involved in AD research. Their involvement can be through directly funding research or supporting research, for example, by charting the research roadmap for the disease, or collecting tissue samples. This analysis includes only organizations with some research focus; organizations that are involved solely in patient support or advocacy are not included.

This profile includes five research funding organizations (Figure 14). Organizations whose mission is to fund one specific research center are not included here. Among research funding organizations profiled here, the Alzheimer’s Association stands out in terms of its research grant budget, which is larger than the combined research budgets of all other organizations identified. However, there are multiple organizations that have annual grant budgets of more than $1 million. Some groups focus on specific research areas, such as genetics or drug discovery, reflecting the diversity of the research spectrum.

Key Organizations

Alzheimer’s Association

Incorporated in 1980 as the Alzheimer’s Disease and Related Disorders Association, the Alzheimer’s Association is a voluntary health organization dedicated to Alzheimer’s research, support, care, and education. Its mission is “to eliminate Alzheimer’s disease through the advancement of research; to provide and enhance care and support for all affected; and to reduce the risk of dementia through the promotion of brain health.” It has a national office in Chicago, along with nationwide presence through a network of 77 chapters. Providing research funding is one of the key activities of the Alzheimer’s Association. Research grants accounted for $25.6 million, or 28 percent of total expenses, in 2007. In addition to directly funding research, the organization also emphasizes its role as a nonprofit entity, focusing on building collaboration and leveraging resources for research advancement. It also has multiple activities focusing on strengthening the AD research community, including organizing scientific meetings, publishing a journal, and building...
a professional society. In addition, the Association is also active in providing support to patient support, increasing public awareness on AD, providing information for healthcare professionals, and advocacy efforts.

**American Health Assistance Foundation**

Founded in 1973, the American Health Assistance Foundation is based in Clarksburg, Maryland. It is dedicated to “funding research seeking cures for Alzheimer’s disease, macular degeneration and glaucoma, and providing information about risk factors, preventative lifestyles, available treatments, and coping strategies for those diseases.” Its AD research program was initiated in 1985. In 2007, its research grant budget amounted to $9.5 million, or 37 percent of total expenses; research grants for AD amounted to $5.2 million. The research grant program focuses on providing seed funding for pilot projects and developing young scientists. The Foundation also provides information for caregivers of AD.

**Cure Alzheimer’s Fund**

Cure Alzheimer’s Fund is a relatively young organization founded in 2004. Based in Wellesley Hills, Massachusetts, its mission is “to fund research with the highest probability of slowing, stopping, or reversing Alzheimer's disease.” Instead of funding investigator-initiated project proposals, the Fund’s Research Consortium selects the researchers that are aligned with its research agenda and solicits proposals directly. In 2007, research grants amounted to $2.4 million, or 82 percent of total expenses. The Fund’s research approach is to identify all genes associated with late-onset AD, clarify their roles, and facilitate treatment development based on the knowledge derived. The Fund does not support indirect costs of the grant recipient’s institution, and all administrative costs are funded by the founders.

**Alzheimer’s Drug Discovery Foundation**

Based in New York City, the Alzheimer’s Drug Discovery Foundation was founded in 2004 as an affiliate to the Institute for the Study of Aging, a private foundation of the Estee Lauder family founded in 1998. The private and public arms of the organization work together toward a single mission: “supporting scientists pursuing drug discovery research for Alzheimer’s disease, related dementias and cognitive aging.” The Foundation views itself as “the only public charity solely dedicated to rapidly accelerating the discovery and development of drugs to prevent, treat and cure AD and cognitive aging.” The organization funds both academic and industry scientists in early drug development, and also hosts the International Conference on Alzheimer’s Disease Drug Discovery annually. In 2007, its grants amounted to $2.1 million, or 59 percent of total expenses, when the financials of the public and private arms are combined.

**The John Douglas French Alzheimer’s Foundation**

Based in Los Angeles, the John Douglas French Alzheimer’s Foundation was founded in 1983 in memory of Dr. John Douglas French, founder and former director of the UCLA Brain Research Institute. Its mission is “to provide seed money for promising research and scientists in the State of California who might not otherwise be funded...to support cutting edge research, individually or in a collaborative effort, which can expedite the day when we might delay the onset and advancement, and find a cure for Alzheimer’s.” In 2007, the Foundation awarded grants totaling $1.4 million,
accounting for 75 percent of its total expenses. In addition to providing seed money, the Foundation encourages collaborative studies; examples include support for consortiums of AD academic research centers such as the University Consortium for Alzheimer’s Research Excellence and the Western Consortium for Alzheimer’s Research Excellence, as well as the Collaboration for Ultimate Research Excellence, focusing on neuroprotection and degeneration.
## Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>ADC</td>
<td>Alzheimer’s Disease Centers</td>
</tr>
<tr>
<td>ADCS</td>
<td>Alzheimer’s Disease Cooperative Study</td>
</tr>
<tr>
<td>ADNI</td>
<td>Alzheimer’s Disease Neuroimaging Initiative</td>
</tr>
<tr>
<td>AlzForum</td>
<td>Alzheimer Research Forum</td>
</tr>
<tr>
<td>APP</td>
<td>Amyloid Precursor Protein</td>
</tr>
<tr>
<td>CAGR</td>
<td>Compound Annual Growth Rate</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CMS</td>
<td>Centers for Medicare &amp; Medicaid Services</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-Adjusted Life Years</td>
</tr>
<tr>
<td>DIAN</td>
<td>Dominantly Inherited Alzheimer Network</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FDG PET</td>
<td>FluroDeoxyGlucose Positron Emission Tomography</td>
</tr>
<tr>
<td>J&amp;J</td>
<td>Johnson &amp; Johnson</td>
</tr>
<tr>
<td>MCI</td>
<td>Mild Cognitive Impairment</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-Mental Status Examination</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NACC</td>
<td>National Alzheimer’s Coordinating Center</td>
</tr>
<tr>
<td>NIA</td>
<td>National Institute on Aging</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NIAGADS</td>
<td>NIA Genetics of Alzheimer’s Disease Data Storage</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PiB</td>
<td>Pittsburgh Compound B</td>
</tr>
</tbody>
</table>
Glossary

**Acetylcholine:** A neurotransmitter released at autonomic synapses and neuromuscular junctions, active in the transmission of nerve impulses, and formed enzymatically in the tissues from choline.

**Adjuvant:** A substance enhancing the immune response to an antigen.

**Adjuvant therapy:** An additional therapy that enhances the effectiveness of a medical treatment.

**Amyloid precursor protein (APP):** A transmembrane protein from which beta-amyloid is derived by proteolytic cleavage by secretases.

**ApoE (Apolipoprotein E):** The APOE gene provides instructions for making a protein called apolipoprotein E. This protein combines with fats (lipids) in the body and is known as a lipoprotein. There are at least three slightly different versions (alleles) of the APOE gene. The major alleles are called e2, e3, and e4. The most common allele is e3, which is found in more than half of the population.

**Atherosclerosis:** Atherosclerosis is characterized by atheromatous deposits in and fibrosis of the inner layer of the arteries. Arteriosclerosis is a chronic disease characterized by abnormal thickening and hardening of the arterial walls with resulting loss of elasticity.

**Atypical antipsychotic drug:** Second-generation drugs to treat psychosis.

**Axon:** A nerve-cell process that usually conducts impulses away from the cell body.

**Beta-amyloid:** An amyloid that is derived from amyloid precursor protein and is the primary component of plaques characteristic of Alzheimer's disease; also called amyloid beta-protein, beta-amyloid protein.

**Beta-secretase:** One of the enzymes that cleave APP. APP can be cleaved by alpha-, beta-, or gamma-secretases. Action of beta- and gamma-secretases result in the type of beta-amyloid associated with AD.

**Biomarker:** A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention.

**Cell cycle:** The complete series of events from one cell division to the next

**Cerebral cortex:** The convoluted surface layer of gray matter of the cerebrum that functions chiefly in coordination of sensory and motor information.
Cerebrospinal fluid: A liquid that is comparable to serum but contains less dissolved material, and is secreted from the blood into the lateral ventricles of the brain. This fluid maintains uniform pressure within the brain and spinal cord.

Cholinesterase: An enzyme that occurs especially in some nerve endings and in the blood and promotes the hydrolysis of acetylcholine.

Dementia: A usually progressive condition (such as Alzheimer’s disease) marked by the development of multiple cognitive deficits, such as memory impairment, aphasia, and inability to plan and initiate complex behavior.

Down’s Syndrome: A congenital condition characterized by moderate to severe mental retardation, slanting eyes, a broad short skull, broad hands with short fingers, and by trisomy of the human chromosome numbered 21.

Dystrophy: A condition produced by faulty nutrition.

Entorhinal cortex: The part of the cerebral cortex in the medial temporal lobe that serves as the main cortical input to the hippocampus.

Enzyme: Any of numerous complex proteins that are produced by living cells and catalyze specific biochemical reactions at body temperatures.

Etiology: The cause or causes of a disease or abnormal condition.

Excitotoxicity: The impact resulting from the action of an agent that binds to a nerve cell receptor, stimulates the cell, and damages it or causes its death.

FDG: Abbreviation for fluorodeoxyglucose, used as an imaging agent in PET scanning.

Free radical: An especially reactive atom or group of atoms that has one or more unpaired electrons. It usually refers to those produced in the body by natural biological processes or introduced from outside (as in tobacco smoke, toxins, or pollutants) and that can damage cells, proteins, and DNA by altering their chemical structure.

Gamma-secretase: One of the enzymes that cleave APP. APP can be cleaved by alpha-, beta-, or gamma-secretases. Action of beta- and gamma-secretases result in the type of beta-amyloid associated with AD.

Geriatrician: A specialist in geriatry, a branch of medicine that deals with the problems and diseases of old age and aging people.

Glutamate: A salt or ester of levorotatory glutamic acid that functions as an excitatory neurotransmitter.
Hippocampus: A curved elongated ridge that is an important part of the limbic system, and is involved in forming, storing, and processing memory.

MEOX2: This gene encodes a protein which may play a role in the regulation of vertebrate limb myogenesis. Mutations in the related mouse protein may be associated with craniofacial and/or skeletal abnormalities, in addition to neurovascular dysfunction observed in Alzheimer's disease.

Microtubule: Any of the minute tubules in eukaryotic cytoplasm that are composed of the protein tubulin and form an important component of the cytoskeleton, mitotic spindle, cilia, and flagella.

Mild cognitive impairment: A condition in which a person has problems with memory, language, or another mental function severe enough to be noticeable to other people and to show up on tests, but not serious enough to interfere with daily life.

Mitochondrion: Any of various round or long cellular organelles of most eukaryotes that are found outside the nucleus, produce energy for the cell through cellular respiration, and are rich in fats, proteins, and enzymes.

Monoclonal antibody: An antibody derived from a single cell in large quantities for use against a specific antigen.

MRI (magnetic resonance imaging): A noninvasive diagnostic technique that produces computerized images of internal body tissues and is based on nuclear magnetic resonance of atoms within the body induced by the application of radio waves.

Neuromodulator: A substance other than neurotransmitter (as a polypeptide) that potentiates or inhibits the transmission of a nerve impulse but is not the actual means of transmission itself.

Neuron: One of the cells that constitute nervous tissue, that have the property of transmitting and receiving nervous impulses. Neurons are highly differentiated frequently as multiple dendrites or usually as solitary axons and conduct impulses toward and away from the nerve cell body.

Neurotransmitter: A substance (as norepinephrine or acetylcholine) that transmits nerve impulses across a synapse.

Nicotinic receptor: Receptors on a neuron that can be stimulated to produce more acetylcholine in the brain.

NMDA receptor: A neurotransmitter receptor, named after N-methyl D-aspartate, an agonist of the receptor. Overstimulation of an NMDA receptor can lead to excess calcium in the neuron.

Parkinson's disease: A chronic progressive neurological disease chiefly of later life that is linked to decreased dopamine production and is marked especially by tremor of resting muscles, rigidity, slowness of movement, impaired balance, and a shuffling gait.
Passive vaccination: Vaccination aiming to create immunity by transfer of antibodies (as by injection of serum from an individual with active immunity).

Personalized medicine: The use of individual patient's genomic information to improve the diagnosis of disease, as well as the prevention and treatment of disease.

PET (positron-emission tomography): An imaging technique where a cross-sectional image of regional metabolism is obtained by a usually color-coded cathode-ray tube representation of the distribution of gamma radiation given off in the collision of electrons in cells with positrons emitted by radionuclides incorporated into metabolic substances.

Plaque: A localized abnormal patch on a body part or surface. A histopathologic lesion of brain tissue that is characteristic of Alzheimer's disease and consists of a dense proteinaceous core composed primarily of beta-amyloid that is often surrounded and infiltrated by a cluster of degenerating axons and dendrites; also called senile plaque.

Progestin: A synthetic progesterone.

PSA (puromycin-sensitive aminopeptidase): A zinc metallopeptidase that hydrolyzes amino acids from the N-terminus of its substrate. This enzyme degrades enkaphalins in the brain, and studies in mice suggest that it is involved in proteolytic events regulating the cell cycle.

Selegiline: The levorotatory form of the monoamine oxidase inhibitor deprenyl that is administered as an adjuvant to therapy using the combination of L-dopa and carbidopa in the treatment of Parkinson's disease and is sometimes used alone to treat endogenous depression or to treat dementia associated with Alzheimer's disease.

SORL1: This gene encodes multiple proteins, and it is strongly expressed in the central nervous system. Recent research found that certain variants of this gene are related to increased production of beta-amyloid.

Statin: Any of a group of drugs (as lovastatin and simvastatin) that inhibit the synthesis of cholesterol and promote the production of LDL-binding receptors in the liver resulting in a usually marked decrease in the level of LDL and a modest increase in the level of HDL circulating in blood plasma.

Tangle: A pathological accumulation of paired helical filaments composed of abnormally formed tau protein that is found chiefly in the cytoplasm of nerve cells of the brain and especially the cerebral cortex and hippocampus and that occurs typically in Alzheimer's disease.

Tau protein: A protein that binds to and regulates the assembly and stability of neuronal microtubules and that is found in an abnormal form as the major component of neurofibrillary tangles.

Thrombosis: The formation or presence of a blood clot within a blood vessel.
References

Articles, Books, and Reports


• Callahan, Christopher. 2006. “Effectiveness of Collaborative Care for Older Adults with Alzheimer’s Disease in Primary Care: A Randomized Controlled Trial,” Journal of American Medical Association, 295(18).


• “Roche and GE Healthcare Collaborate to Develop Personalized Medicine for Alzheimer’s Patients,” *MTB Europe*, July 11, 2005.


Data Sources

- Additional sources include various presentations and abstracts from International Conference on Alzheimer's Disease 2008, company Web sites, annual reports, and SEC filings for various years; nonprofit organization Web sites and IRS form 990s for various years, accessed January 2009.