Alzheimer’s Disease: A Look at Current and Future Treatment Options

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Spring 2014

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TO THE UNIVERSITY HONORS COLLEGE:

As thesis advisor for HALEIGH MILLER,

I have read this paper and find it satisfactory.

[Signature]
Thesis Advisor

3-24-2014
Date
Précis

Alzheimer’s disease (AD) is the most common form of dementia known today, with more than 5.2 million people suffering from this condition in the United States alone. This number is expected to rise to approximately 13.8 million by 2050 unless therapies effective in slowing or preventing the disease are developed. There are currently five FDA-approved medications for the treatment of AD symptoms. Four of these medications fall into a class of drugs known as cholinesterase inhibitors. The fifth medication, memantine, falls into a separate drug class. Because these two classes of drugs have significantly different effects on the body, they can be used together in what is known as combination therapy.

The overall goal of this project was to determine whether combination therapy is more effective than cholinesterase monotherapy for treating AD and to identify new types of AD medications that are currently under development. In order to answer these questions, a literature review was conducted. This literature review focused on information from the National Institute of Health, Alzheimer’s Association, and peer-reviewed journals that were published in the last ten years.

As a pre-pharmacy student, the ways in which prescription medications are used to manage AD is of great interest to me. My choice to pursue this as a topic for my Honors thesis was solidified by the fact that my grandmother, Loni Miller, has been suffering from AD for many years.

Ultimately, the studies cited in this review did not provide conclusive evidence about the effectiveness of combination therapy in relation to cholinesterase monotherapy. Variation in the results produced by different efficacy scales and by different research studies illustrates
the need for further research on the effectiveness of combination therapy in AD treatment. In addition to therapeutic effectiveness, which was the focus of this review, it was also noted that cost-effectiveness, safety, side effects, and clinical significance must be taken into account before the overall effectiveness of combination therapy can be assessed.

Uncertainty about the true cause of AD has led to great diversity in the AD treatments that are currently under development. Some experimental drugs are being developed as add-on therapies for the AD medications that are currently available, while others are being developed in hopes of preventing or reversing the damage that is evident in the brains of people with AD. Unfortunately, however, the future of AD treatment does not look promising. Although hundreds of AD drugs are currently under development, a major change in the way that AD is treated appears to be many years away.

Additional funding for AD research is desperately needed in order to provide scientists with the resources that they need to combat this cruel disease. My hope is that reviews such as this will help to spread the word about AD and emphasize the importance of giving this disease the attention and funding that it deserves.
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Alzheimer’s Disease: An Introduction

Alzheimer’s disease (AD) is the most common form of dementia known today.\(^1\) The term “dementia” refers to a variety of conditions that arise from a loss of nerve cell function and/or nerve cell death in the brain, including Alzheimer’s disease, vascular dementia, Parkinson’s disease dementia, Creutzfeldt-Jakob disease and other types of mixed dementia.\(^1\) AD was first identified as a form of dementia in 1906 and accounts for approximately 60-80% of all dementia cases.\(^1,2\)

Symptoms

A seven-stage framework for rating AD symptoms can be seen in Table 1. This system was developed by Barry Reisberg, M.D., clinical director of the New York University School of Medicine’s Silberstein Aging and Dementia Research Center.\(^3\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Severity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No Impairment</td>
<td>The person does not experience any memory problems. An interview with a medical professional does not show any evidence of symptoms of dementia.</td>
</tr>
<tr>
<td>2</td>
<td>Very Mild Decline</td>
<td>The person may feel as if he or she is having memory lapses — forgetting familiar words or the location of everyday objects. However, no symptoms of dementia can be detected during a medical examination or by friends, family or co-workers.</td>
</tr>
</tbody>
</table>
| 3     | Mild Decline           | • Difficulty coming up with the right word/name  
• Difficulty performing tasks in social or work settings  
• Forgetting material that they have just read  
• Losing or misplacing a valuable object  
• Increasing difficulty with planning or organizing |
| 4     | Moderate Decline       | • Forgetfulness of recent events  
• Greater difficulty planning dinner for guests, paying bills or managing finances  
• Forgetfulness about their own personal history  
• Becoming moody or withdrawn, especially in socially or mentally challenging situations |
| 5     | Moderately Severe Decline | • Unable to recall their own address, telephone number, high school/college from which they graduated, etc.  
• Becoming confused about where they are or what day it is  
• Need help choosing proper clothing for the season or the occasion  
• Still remember significant details about themselves and their family  
• Still require no assistance with eating or using the toilet |
Table 1. Seven Stages of Alzheimer's disease.¹

Causes

The majority of experts believe that AD does not result from a single cause but from a variety of different contributing factors. Research indicates that some of these factors include brain changes that begin 20 or more years before symptoms appear.¹ Five key factors that are believed to be correlated with AD include accumulation of beta-amyloid, accumulation of the protein tau, protein misfolding, loss of nicotinic acetylcholine receptors, and genetic mutations.⁴ The summative effect of these changes on the brain can be seen in Figure 1.
Beta-amyloid

Beta-amyloid is a protein fragment that has been linked to Alzheimer’s disease by many research studies, including a study by Wang et al. which found that AD brains are characterized by a marked shift from the predominately soluble pools of beta-amyloid seen in normal brains to very large pools of insoluble beta-amyloid. In autopsies performed on individuals with a clinical diagnosis of AD, it is generally found that plaques composed of extracellular deposits of insoluble beta-amyloid peptides have formed (Fig. 2). This has led to the hypothesis that accumulation of beta-amyloid during the preclinical stage of AD initiates a cascade of events. These events ultimately lead to synaptic dysfunction and neuron loss and/or atrophy within the temporoparietal and hippocampal regions of the brain. It is believed that these degenerative changes to the brain contribute to cognitive decline in patients with AD.
Protein Tau

The major biological function of the protein tau is to stimulate microtubule assembly and stabilize microtubule structure. In individuals with AD, tau undergoes several abnormal post-translational modifications which lead to the accumulation of neurofibrillary tangles and neurofibrillary degeneration (Fig. 2). One of the most common post-translational modifications seen in AD patients is hyperphosphorylation of the tau protein.8

Protein Misfolding

Although soluble beta-amyloid proteins are normal components of brain tissue, accumulation of insoluble beta-amyloid into plaques is characteristic of AD. It is believed that these plaques form due to the misfolding of beta-amyloid proteins. In soluble beta-amyloid proteins, hydrophobic amino acids are folded deep inside the protein; however, when protein misfolding occurs, these hydrophobic groups may be found on the exterior of the protein.
molecule. This exposure not only makes the beta-amyloid insoluble but also allows one insoluble molecule to bind to another, thereby allowing the formation of the insoluble plaques observed in AD patients.\textsuperscript{11}

**Loss of Nicotinic Acetylcholine Receptors**

AD is ultimately characterized by a loss of nerve cells (neurons) in the brain, generally due to the beta-amyloid plaques and neurofibrillary tangles previously discussed. This loss is most frequent in neurons that express nicotinic acetylcholine receptors—receptors that are regulated by the binding of a neurotransmitter known as acetylcholine.\textsuperscript{12} Acetylcholine is a chemical messenger in the brain that transmits signals between neurons at a neuronal junction known as a synapse (Fig. 3).

After the transmission is complete, an enzyme referred to as acetylcholinesterase breaks down acetylcholine so that it can be recycled. In AD, the cells that produce acetylcholine are damaged or destroyed. This results in a reduced number of acetylcholine molecules that are able to serve as neurotransmitters. Without an adequate number of

\textsuperscript{13}
acetylcholine molecules, communication between neurons cannot effectively occur. Communication between neurons is also reduced when neurons expressing nicotinic acetylcholine receptors are damaged or destroyed.\textsuperscript{12} Because acetylcholine signaling pathways are involved with memory, judgment, and other thought processes, a reduction in acetylcholine and/or neurons expressing acetylcholine receptors leads to the cognitive decline associated with AD.\textsuperscript{14}

**Genetic Mutation**

Genetic mutation is the only proven cause of AD; however, this factor is estimated to account for less than 1\% of all AD cases. Three known genetic mutations have been linked to AD. These mutations involve the genes for amyloid precursor proteins, presenilin 1 proteins, and presenilin 2 proteins.\textsuperscript{1} Presenilin 1 and 2 genes are involved with the survival of nerve cells in the brain and the processing of amyloid precursor proteins.\textsuperscript{4} An individual who inherits any of these genes is guaranteed to develop what is referred to as “dominantly inherited” AD. Generally, individuals with dominantly inherited AD develop early-onset AD, which is characterized by disease symptoms that develop before age 65.\textsuperscript{1}

**Prevalence and Mortality**

It is estimated that 5.2 million Americans suffered from AD in 2013, making AD the most common neurodegenerative disease in the United States.\textsuperscript{1} Approximately 5 million of these individuals were age 65 or older. The remaining 200,000 were under age 65 and had been diagnosed with early-onset AD. The breakdown of AD cases by age range can be seen in Table 2. Nearly two-thirds of AD patients in the United States are women, although researchers
believe that this is primarily attributable to the fact that women live longer, on average, than men.¹

By 2050 the number of people age 65 and older who are affected by AD is estimated to reach 13.8 million unless therapies effective in slowing or preventing the disease are developed (Fig. 4). If this prediction holds true, the number of AD patients in this age range will be almost three times greater than the current value of 5 million. This projected increase is based on a variety of factors, including an increase in the number of Americans living into their 80s and 90s and the baby boomer generation’s progression into the age range that is most associated with AD.¹

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Percent of AD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 65</td>
<td>4%</td>
</tr>
<tr>
<td>65 to 74</td>
<td>13%</td>
</tr>
<tr>
<td>75 to 84</td>
<td>44%</td>
</tr>
<tr>
<td>85 or older</td>
<td>38%</td>
</tr>
</tbody>
</table>

Table 2. Estimated percentage of AD patients by age in 2013.¹

Figure 4. Projected number of people age 65 and older in the U.S. population with AD, 2010 to 2050.¹
AD is the sixth-leading cause of death for all ages in the United States and the fifth-leading cause of death for individuals age 65 and older.\textsuperscript{1} It is important to note, however, that these statistics only take into account individuals whose death certificates list AD as the underlying cause of death. Many individuals who suffer from AD ultimately die from acute conditions due to AD-related complications, including immobility, swallowing disorders, and poor nutrition. Pneumonia is one of the mostly commonly identified causes of death in individuals with AD. According to the Center for Disease Control (CDC), 83,494 people died \textit{from} AD in 2010 while approximately 400,000 people died \textit{with} AD in 2010.\textsuperscript{1} Due to the way that cause of death is recorded, the most that can be said is that the actual number of deaths caused by AD in 2010 falls somewhere between these two figures. Overall, 61\% of 70 year olds with AD in the United States are expected to die before age 80 compared to only 30\% of 70 year olds without AD.\textsuperscript{1}

**Treatment**

There are currently five FDA-approved medications for the treatment of AD: Razadyne\textsuperscript{®} (galantamine), Exelon\textsuperscript{®} (rivastigmine), Aricept\textsuperscript{®} (donepezil), Cognex\textsuperscript{®} (tacrine), and Namenda\textsuperscript{®}/Ebixa\textsuperscript{®} (memantine). Although these drugs may prevent the symptoms of AD from becoming worse for a limited period of time, none of these medications have the ability to slow, stop, or reverse the damage done by this disease.\textsuperscript{15} Instead, these medications are generally used to slow cognitive decline and manage behavioral symptoms in AD patients. Galantamine, rivastigmine, donepezil, and tacrine are classified as cholinesterase inhibitors. The fifth drug, memantine, is classified as an N-methyl-D-aspartate (NMDA) antagonist. These two classes of drugs have significantly different mechanisms of action and can be used together
in what is known as combination therapy.\textsuperscript{7} Non-pharmacological treatments, including environment modification and therapeutic interventions (such as physical therapy, occupational therapy, etc.), are also commonly used to treat AD symptoms and behaviors.

\textbf{Cholinesterase Inhibitors}

Cholinesterase inhibitors, also referred to as acetylcholinesterase inhibitors, prevent the breakdown of acetylcholine in the human body by occupying the site where acetylcholine normally attaches to the enzyme acetylcholinesterase (Fig. 5). By blocking the binding site on acetylcholinesterase, cholinesterase inhibitors prevent acetylcholine from interacting with and being metabolized by this enzyme.\textsuperscript{16}

In 1993, tacrine became the first cholinesterase inhibitor to be used therapeutically to treat people with AD; however, tacrine is rarely used today due to its hepatotoxicity (toxicity to the liver). Donepezil, galantamine and rivastigmine are currently used to delay mental deterioration and reduce neuropsychiatric symptoms in patients with AD.\textsuperscript{17} Although all three of these medications are classified as cholinesterase inhibitors, patients may respond differently to each drug due to the pharmacological differences among these medications. Currently, galantamine and rivastigmine are approved for the treatment of mild to moderate AD. Donepezil has recently been approved for the treatment of all stages of AD.\textsuperscript{18}

In addition to AD, cholinesterase inhibitors are also used to treat Parkinson’s disease dementia, glaucoma, schizophrenia, myasthenia gravis, and various types of non-AD dementia. The most common side effects of cholinesterase inhibitors include nausea, vomiting, diarrhea, abdominal pain, bradycardia, anorexia, and dizziness.\textsuperscript{19}
Figure 5. The simplified mechanism of action for cholinesterase inhibitors.\textsuperscript{20}

\textbf{Memantine}

Memantine was approved for use in the United States in 2004 and is currently used to treat moderate to severe cases of AD. As previously mentioned, memantine is classified as an N-methyl-D-aspartate (NMDA) antagonist. Although its mechanism of action in AD is not completely understood, memantine selectively blocks the activation of NMDA-type glutamate receptors in the brain. This selective blocking regulates synaptic stimulation through these
receptors. Although glutamate is a chemical messenger in the brain that is important for learning and memory, it is hypothesized that high levels of glutamate within the central nervous system can overstimulate NMDA receptors and contribute to the neurodegeneration associated with AD. Memantine works to allow beneficial glutamate stimulation in the brain while preventing excessive stimulation of NMDA receptors. Possible side effects of memantine include diarrhea, insomnia, dizziness, headache, and hallucination.21

Combination Therapy

As previously mentioned, the two types of AD medications that are currently available (cholinesterase inhibitors and NMDA antagonists) can be used concurrently in what is referred to as “combination therapy” due to their varying mechanisms of action.7 Although the individual effectiveness of tacrine, galantamine, rivastigmine, donepezil and memantine has been the topic of many research studies in the past, the effectiveness of combination therapy in comparison to monotherapy is still under investigation. Because memantine is a relatively new drug, researchers are still conducting clinical trials in order to determine whether the use of memantine in addition to one of the cholinesterase inhibiting drugs is significantly more effective than the use of cholinesterase inhibitors alone.

Research Questions

1. Is combination therapy more effective than cholinesterase monotherapy for treating Alzheimer’s disease?

2. What other types of Alzheimer’s disease medications are currently under development?
Methodology

A literature review of scholarly articles was conducted in order to gather information about AD and to answer the proposed research questions. The vast majority of the sources utilized in this paper were published within the last ten years in order to ensure that the information provided was current. Each source was carefully analyzed in order to make certain that all of information was gathered from a reputable source for the fields of medicine and pharmacology. In order to ensure that all viewpoints on AD treatment were fairly represented, information was collected from numerous sources.

For background information regarding AD, the Alzheimer’s Association and National Institute of Health were utilized as main sources of information. In order to find primary data comparing combination therapy and monotherapy, various academic databases were systematically searched. These databases included PubMed, MEDLINE, and Web of Science. The research studies cited in this paper were chosen based on their use of the NPI and/or ADCS-ADL inventory to assess treatment efficacy. These efficacy scales were chosen due to the fact that they were most prevalent in articles that compared cholinesterase monotherapy to combination therapy. The five experimental treatments that were discussed in this paper were carefully chosen in order to reflect the variety of AD therapies currently under development.

In addition to the literature review, interviews with Washington State University professors Dr. Joe Harding and Dr. Jay Wright were also conducted. The overall goal of these interviews was to gain information about their research that is not available in the published literature (i.e. expected timeline, most significant challenges, etc.).
The Effectiveness of Current Alzheimer’s Disease Treatment

Studies that analyze the effectiveness of AD treatment generally use one or more efficacy scales to rate patient response based on level of cognition, ability to perform everyday tasks, and/or frequency of behavioral disturbances. Five of the scales commonly used in AD research are described in Table 3. For this review, the effectiveness of combination therapy in comparison to cholinesterase monotherapy will be evaluated using the Neuropsychiatric Inventory (NPI), Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) inventory, and the Weintraub Activities of Daily Living (Weintraub ADL) inventory.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's Disease Cooperative Study - Activities of Daily Living</td>
<td>ADCS-ADL</td>
<td>Evaluates the functional abilities of patients</td>
</tr>
<tr>
<td>Clinician's Interview-Based Impression of Change Plus Caregiver Input</td>
<td>CIBIC-Plus</td>
<td>Evaluates global function (how the patient is functioning in all aspects of their world)</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory</td>
<td>NPI</td>
<td>Measures the frequency and severity of behavioral disturbances</td>
</tr>
<tr>
<td>Severe Impairment Battery</td>
<td>SIB</td>
<td>Evaluates specific behavioral and cognitive deficits associated with severe dementia</td>
</tr>
<tr>
<td>Weintraub Activities of Daily Living</td>
<td>Weintraub ADL</td>
<td>Produces dependency scores from 0% (normal) to 100% (complete dependency)</td>
</tr>
</tbody>
</table>

Table 3. Efficacy scale names, abbreviations, and descriptions.

In this review, the term “monotherapy” refers to treatment with a single cholinesterase inhibitor. Memantine monotherapy will not be discussed. In addition, “combination therapy” is defined as the treatment of AD using memantine and any one of the cholinesterase inhibitors. The specific cholinesterase inhibitor used for each study is noted.

Neuropsychiatric Inventory

The Neuropsychiatric Inventory (NPI) consists of a 12-item interview with a patient’s caregiver that assesses the frequency and severity of twelve behavioral disturbances. These
behavioral disturbances include delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time behavioral disturbances, and/or appetite/eating abnormalities. Based on the scoring system shown in Figure 6, NPI scores range from 0 to 144 with a higher score indicating more severe behavioral symptoms.\textsuperscript{23}

<table>
<thead>
<tr>
<th>Scoring the Neuropsychiatric Inventory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each behavior is rated separately using the following system:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Frequency is rated as:</strong></td>
</tr>
<tr>
<td>1. Rarely – less than once per week</td>
</tr>
<tr>
<td>2. Sometimes – about once per week</td>
</tr>
<tr>
<td>3. Often – several times per week but less than every day</td>
</tr>
<tr>
<td>4. Very often – once or more per day</td>
</tr>
<tr>
<td><strong>Severity is rated as:</strong></td>
</tr>
<tr>
<td>1. Mild – produces little distress in the patient</td>
</tr>
<tr>
<td>2. Moderate – more disturbing to the patient but can be redirected by the caregiver</td>
</tr>
<tr>
<td>3. Severe – very disturbing to the patient and difficult to redirect</td>
</tr>
<tr>
<td><strong>Total Score = Frequency x Severity</strong></td>
</tr>
</tbody>
</table>

Figure 6. The Neuropsychiatric Inventory Scoring System.\textsuperscript{22}

Multiple AD studies have found statistically significant results when using the NPI to compare combination therapy to cholinesterase monotherapy. A 2004 study by Tariot et al. analyzed the effectiveness of combination therapy relative to cholinesterase monotherapy over a 24-week period. For this study, all patients received 5-10 mg of donepezil daily. Patients in the combination therapy group received an initial dose of 5 mg/day of memantine with titration in 5-mg weekly increments to a final dose of 20 mg/day at the beginning of week 4. This dosage level was held constant for the remainder of the study. Although transient dosage adjustments for memantine treatment were permitted from week 3 to week 8 for patients experiencing adverse events, all patients in the combination therapy group were required to
receive the target dose of 20 mg/day by the end of week 8. Patients who were unable to tolerate this dose were disenrolled from the study. Patients in the monotherapy group received placebo treatment in place of memantine.23

Overall, this study by Tariot et al. found that patients treated with combination therapy for 24 weeks had a mean* decrease of 0.1 points based on LOCF analysis†, while those treated with cholinesterase monotherapy had a mean increase of 3.7 points (Table 4). Keeping in mind that a higher score indicates more severe symptoms, these results indicate that the combination therapy group showed mild behavioral improvement over the course of the study while the monotherapy group showed a numerical mean decline (p=0.002). This result was also confirmed using OC analysis‡, with patients in the combination therapy group showing an overall mean decrease of 0.5 points at week 24 compared to an overall mean increase of 2.9 points for patients in the monotherapy group (p=0.01).23

<table>
<thead>
<tr>
<th>Analysis Type</th>
<th>Combination Therapy</th>
<th>Monotherapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCF</td>
<td>-0.1</td>
<td>+3.7</td>
<td>0.002</td>
</tr>
<tr>
<td>OC</td>
<td>-0.5</td>
<td>+2.9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 4. Mean change from baseline of NPI scores at 24 weeks (Tariot et al.)23

A study by Cummings et al. also compared combination therapy and cholinesterase monotherapy using the NPI and found statistically significant results at both 12 and 24 weeks (Table 5, Fig. 7). For this study, all patients received 5-10 mg of donepezil daily. Patients in the combination therapy group received an initial dose of 5 mg/day of memantine with titration in 5-mg weekly increments to a final dose of 20 mg/day at the beginning of week 4. This dosage level was held constant for the remainder of the study. Patients in the monotherapy group

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* “Mean” increase/decrease refers to the change in the least-squares mean score relative to baseline.
† Additional information about Last Observation Carried Forward (LOCF) analysis is provided in the appendix.
‡ Additional information about Observed Case (OC) analysis is provided in the appendix.
received placebo treatment in place of memantine. Information regarding dosage adjustments for patients experiencing dose-related adverse events was not provided.24

After the first 12 weeks of this study, the mean NPI score produced by LOCF analysis decreased by 2.5 points for patients receiving combination therapy, while the mean score for those receiving monotherapy increased by 1.7 points (p<0.001). After 24 weeks, patients receiving combination therapy had returned to near baseline levels, with an overall mean decrease of 0.1 points compared to initial NPI scores. Patients receiving monotherapy increased a mean total of 3.7 points from baseline measurements in the same time period. The reduced decline in patients receiving combination therapy was found to be statistically significant (p=0.002). The same overall pattern was also evident in data produced by OC analysis. After 12 weeks, the mean score for combination therapy patients decreased by 3.0 points, and the mean score for monotherapy patients increased by 1.4 points (p<0.001). After 24 weeks, the mean score for combination therapy patients decreased by 0.5 points, and the mean score for monotherapy patients increased by 2.9 points (p=0.01). As shown in Figure 8, the NPI domains that exhibited the greatest variability between the two therapy groups in the study by Cummings et al. (based on LOCF analysis) included agitation/aggression, nighttime behavior, and irritability/lability.24

<table>
<thead>
<tr>
<th>Analysis Type</th>
<th>Combination Therapy</th>
<th>Monotherapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 12</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOCF</td>
<td>-2.5</td>
<td>+1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OC</td>
<td>-3.0</td>
<td>+1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOCF</td>
<td>-0.1</td>
<td>+3.7</td>
<td>0.002</td>
</tr>
<tr>
<td>OC</td>
<td>-0.5</td>
<td>+2.9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 5. Least-squares mean change from baseline of NPI scores at 12 and 24 weeks (Cummings et al.)24
A study published in June 2013 by Grossberg et al. also found a statistically significant difference between combination therapy and cholinesterase monotherapy using the NPI (Table 6, Fig. 9). For this study, all patients received a stable dose of a cholinesterase inhibitor (specific details were not provided). Patients in the combination therapy group received an initial dose of 7 mg/day of memantine with titration twice-weekly in 7 mg increments to a
target dose of 28 mg/day at the beginning of week 4. By week 8, all patients in the combination therapy group required to tolerate at least 21 mg of memantine per day. Participants who were unable to tolerate this dose were disenrolled from the study. Patients in the monotherapy group received placebo treatment in place of memantine.26

After 24 weeks of treatment, the mean NPI score for patients receiving combination therapy decreased by 4.3 points based on LOCF analysis, while the mean score for patients receiving cholinesterase monotherapy decreased by 1.6 points (p=0.005). Keeping in mind that a higher score indicates more severe symptoms, this data suggests that both treatment groups showed a small mean improvement in NPI scores over the course of the study. Data from OC analysis was not reported.26

<table>
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<td>Change from Baseline</td>
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</table>

Table 6. Mean change from baseline of NPI scores at 24 weeks based on LOCF analysis (Grossberg et al.)26

Figure 9. Least-squares mean change from baseline of NPI scores at 24 weeks (Grossberg et al.)26

In contrast to the aforementioned studies, a 24-week study by Porsteinsson et al. found no statistically significant differences in the NPI scores for the monotherapy and combination
therapy groups (Table 7). For this study, all patients received a stable dose of donepezil, rivastigmine, or galantamine. Patients in the combination therapy group received an initial dose of 5 mg/day of memantine with titration in 5-mg weekly increments to a final dose of 20 mg/day at the beginning of week 4. This dosage level was held constant for the remainder of the study; however, dose adjustments were permitted from week 3 to week 8 for participants experiencing adverse events. Patients in the monotherapy group received placebo treatment in place of memantine.25

At the end of this 24-week study, the mean NPI scores increased by 1.1 points and 0.3 points for the combination therapy and monotherapy groups, respectively, based on LOCF analysis (p=0.743). Data produced by OC analysis gave a slightly different result for this study, with the mean score for patients receiving combination therapy increasing by 0.5 points by week 24 and the mean score for patients receiving cholinesterase monotherapy decreasing by 0.4 points (p=0.985).25

<table>
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<th>Monotherapy</th>
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</thead>
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<td>0.743</td>
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<td>OC</td>
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</tr>
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</table>

Table 7. Mean change from baseline of NPI scores at 24 weeks (Porsteinsson et al.)25

**Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory**

The Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) inventory is a 42-point questionnaire that is used to evaluate the functional abilities of patients with AD. Although some studies utilize the entire inventory, most select key points that pertain to AD patients, such as level of independence while walking, eating, grooming, using the telephone, or communicating. When the ADCS-ADL inventory is evaluated, higher scores
indicate greater functional ability. A page from a sample version of the ADCS-ADL can be found in the appendix.

The previously mentioned study by Tariot et al. found statistically significant results when comparing combination therapy and cholinesterase monotherapy using a 19-point ADCS-ADL inventory (Table 8, Fig. 10). After 24 weeks, the mean ADCS-ADL score for patients receiving combination therapy decreased by 2.0 points based on LOCF analysis, while the mean score for patients receiving cholinesterase monotherapy decreased by 3.4 points (p=0.03). The same pattern was seen in the data produced by OC analysis, with patients in the combination therapy group decreasing by a mean score of 1.7 points and patients in the monotherapy group decreasing by a mean score of 3.3 points (p=0.02).

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<td>OC</td>
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Table 8. Least-squares mean change from baseline of ADCS-ADL scores at 24 weeks (Tariot et al.)

Figure 10. Mean ADCS-ADL score by visit and at end point (Tariot et al.)
Two more recent ADCS-ADL inventory studies have produced results that do not support those obtained by Tariot et al. The aforementioned study by Grossberg et al. which produced statistically significant results using the NPI did not produce statistically significant results using the ADCS-ADL inventory (Table 9, Fig. 11). The mean ADCS-ADL score for patients receiving combination therapy decreased by 0.7 points based on LOCF analysis, while the mean score for patients receiving monotherapy decreased by 1.3 points (p=0.117). Data from OC analysis was not reported.26

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<tr>
<td>Change from Baseline</td>
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Table 9. Mean change from baseline of ADCS-ADL scores at 24 weeks based on LOCF analysis (Grossberg et al.)26

The aforementioned study by Porsteinsson et al. that failed to find statistically significant results using the NPI also failed to do so using the ADCS-ADL inventory (Table 10, Fig. 12). For this 24 week trial, the mean ADCS-ADL score for patients receiving combination therapy decreased by 2.9 points based on LOCF analysis, while the mean score for patients receiving cholinesterase monotherapy decreased by 2.8 points (p=0.816). Data produced by OC
analysis showed a slightly different pattern. Although the mean score for patients receiving combination therapy once again decreased by 2.9 points, the mean score for patients receiving cholinesterase monotherapy decreased by only 1.2 points (p=0.741).  

<table>
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<td>0.741</td>
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Table 10. Mean change from baseline of ADCS-ADL scores at 24 weeks (Porsteinsson et al.)

Weintraub Activities of Daily Living

The Weintraub Activities of Daily Living (Weintraub ADL) inventory is based on 31 questions that are answered by a patient’s spouse and/or caregiver. These questions are very similar to those used for the ADCS-ADL inventory. The Weintraub ADL is scored using a percentage scale; scores range from 0% (normal) to 100% (complete dependency).

The longest duration study to date of AD combination therapy supports the notion that combination therapy is more effective than cholinesterase monotherapy. This study by Atri et al. collected data over a period of four years and utilized the Weintraub ADL inventory as one
method for measuring patient response to treatment. In order to account for variation in certain patient demographics (baseline score, age, education, and duration of illness), regression modeling was used to analyze data from this study. Thus, the given data points are predictions based on the best-fit regression model for the obtained data. For this study, all patients received a stable dose of donepezil, galantamine, or rivastigmine. Patients in the combination therapy group also received memantine; however, the dosage level was not standardized. Patients in the monotherapy group did not receive a placebo.27

Overall, this study produced statistically significant results during all years except year one (Table 11). During year one, the model-predicted Weintraub ADL scores were 32.4% and 35.7% for combination therapy and cholinesterase monotherapy, respectively. Although these scores indicate that monotherapy patients were more dependent, on average, than combination therapy patients after one year of treatment, this difference was not statistically significant (p>0.05). For years two through four, the model-predicted dependency scores for the combination therapy group were significantly lower than the scores for the monotherapy group (p≤0.01). As shown in Figure 13, the rise in model-predicted dependency scores over the course of this study was significantly greater for the monotherapy group than for the combination therapy group. This suggests that combination therapy prevents disease progression. This pattern has not been documented in other published studies, possibly due to the short-term nature of most AD trials.27

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<tr>
<td>1</td>
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<td>35.7%</td>
<td>&gt;0.05</td>
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<tr>
<td>2</td>
<td>41.2%</td>
<td>49.5%</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>49.4%</td>
<td>62.6%</td>
<td>0.001</td>
</tr>
<tr>
<td>4</td>
<td>56.9%</td>
<td>75.0%</td>
<td>0.001</td>
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</table>

Table 11. Model-predicted Weintraub ADL scores by year (Atri et al.)27
Discussion

The effectiveness of combination therapy as measured by the NPI and ADCS-ADL is still unclear. As previously stated, studies by Tariot et al., Cummings et al., and Grossberg et al. produced data which indicated a statistically significant difference between combination therapy and cholinesterase monotherapy using the NPI, especially in regards to agitation/aggression, nighttime behavior, and irritability/lability. However, a study by Porsteinsson et al. failed to replicate these findings. Although the study by Tariot et al. also found statistically significant improvements with combination therapy using the ADCS-ADL inventory, the studies by Grossberg et al. and Porsteinsson et al. failed to achieve statistical significance using this efficacy scale. The lack of consistent findings produced by different research studies and efficacy scales makes it clear that further research is needed to make a definitive conclusion about the effectiveness of combination therapy relative to cholinesterase monotherapy.

Although the results produced by Atri et al. indicated that over time combination therapy becomes increasingly more effective than cholinesterase monotherapy at preventing
disease progression, this result has not been replicated by any other research studies to date. Thus, additional long-term clinical trials are needed before the therapeutic effectiveness of combination therapy can ultimately be determined.

Even if all studies to date had shown a statistically significant difference in the therapeutic effectiveness of combination therapy when compared to cholinesterase monotherapy, further research would still be necessary. This is due to the fact that many other important factors, including cost effectiveness, safety, and side effects must be taken into account before any hard conclusions can be made about the overall effectiveness of a therapy regimen.

Because the focus of this review was on the therapeutic effectiveness of combination therapy, two important limitations of the presented data need to be addressed. Firstly, the data in this review was analyzed based on statistically significant differences between the least-squares mean scores relative to baseline; however, a comparison was not made between the baseline scores of the two treatment groups or the baseline scores of the various studies that were cited. Due to the fact that some AD drugs may work better in people with better baseline function, future reviews of this kind should utilize only studies with similar baseline scores, if possible. The similarity of baseline scores was not taken into account in this review due to the already limited availability of data comparing combination therapy to cholinesterase monotherapy.

§ The studies cited in this review did not find any statistically significant data to suggest that combination therapy causes more side effects than cholinesterase monotherapy.
In addition, all of the studies that were cited in this review used only statistical significance to measure the effectiveness of combination therapy. Statistical significance refers to a difference between two measurements that results from more than random chance. Although expressing statistical significance in the form of a p-value is an important aspect of nearly all statistical analyses, the correlation between statistical significance and clinical significance has been questioned by many clinical researchers. Clinical significance refers to the “practical effectiveness” of a drug. One way of defining clinical significance is by setting a Minimal Important Difference (MID) which has been defined as “the smallest difference in the score of a domain of interest that patients perceived as beneficial and which would lead, in the absence of troublesome side effects and/or excessive cost, to a change in management.”

One published study that attempted to determine an MID for dementia studies reported that Canadian geriatricians and neurologists felt that a change of at least 3.72 points on a 161 point scale was necessary for there to be a noticeable change in overall symptoms. Although no MID has officially been set for AD studies, if applied to the studies discussed in this review, the MID calculated in the previously mentioned study would indicate that the majority of statistically significant results discussed in this review are not clinically significant. Thus, it is important to note that much more than statistical significance must be taken into account when ultimately determining whether one type of AD treatment is more effective than another.

The Future of Alzheimer’s Disease Treatment

Before reaching U.S. markets, all drugs must be approved by the Food and Drug Administration (FDA). The drug development and approval process in the United States is extremely expensive, with an average cost of $329 million per drug. This process is very time
consuming as well, with the average drug taking approximately 12 years to move from the research laboratory to the pharmacy shelf.\textsuperscript{30}

According to the FDA, the drug development and approval process consists of the following stages:\textsuperscript{30}

1. Preclinical Research
2. Investigational New Drug (IND) Application
3. Phase I Trials
4. Phase II Trials
5. Phase III Trials
6. New Drug Application (NDA)
7. Approval
8. Phase IV Trials (used to study long-term side effects)

Government records indicate that only five drugs per 5,000 that begin preclinical testing ever reach human trials. On average, only one of these five drugs is ever approved by the FDA.\textsuperscript{30} For AD medications specifically, 101 attempts to develop new drugs failed between 1998 and 2011. During this same thirteen year span, only three AD drugs received FDA approval, indicating a success ratio of approximately 1 in 34.\textsuperscript{31} The distribution of successful and unsuccessful AD drug candidates throughout this time period is shown in Figure 14. The most recently developed AD drug, memantine, was approved by the FDA on October 16, 2003.\textsuperscript{32}

According to the FDA, nearly 100 medications for AD and other dementias are currently in clinical trials or under FDA review.\textsuperscript{31} This group of experimental drugs contains a great deal of variety in both mechanism of action and intended effect. A portion of the AD drugs that are currently under development are intended to be used to lessen AD symptoms and slow progression, much like the five AD medications that are currently available. Other experimental drugs, however, have the potential to prevent, stop, and even reverse the damage done by AD.
Figure 14. Alzheimer’s Drugs in Development, 1998 to 2011. 31

The following sections are intended to provide readers with a brief overview of a few AD medications that are currently under development. These five medications were identified through recent press releases and chosen in order to illustrate the diversity of drug products currently under investigation.

**Lu AE58054**

Lu AE58054 is an experimental AD drug that is currently under joint development by two pharmaceutical companies, Lundbeck and Otsuka. As of January 2014, Lu AE58054 is undergoing four final-stage Phase III clinical trials with an experimental population of approximately 3,000 patients from 17 different countries. These clinical trials are expected to last three years, and if successful, Lundbeck and Otsuka hope to have Lu AE58054 on the market in 2017. 33
According to Lundbeck and Otsuka, Lu AE58054 is being developed as an add-on medication for cholinesterase inhibitor therapy, not as a stand-alone AD drug.\textsuperscript{34} Lu AE58054 is taken orally and is an antagonist of the 5-HT\textsubscript{6} receptor (also known as the serotonin 6 receptor) which is primarily expressed in the brain. Researchers hypothesize that 5-HT\textsubscript{6} receptors in the cerebral cortex and hippocampal regions of the brain contribute to the cognitive decline associated with AD. To combat this, 5-HT\textsubscript{6} receptor antagonists, such as Lu AE58054, enhance the neurotransmission of acetylcholine, glutamate, noradrenaline and dopamine.\textsuperscript{34} Lundbeck and Otsuka’s focus on the 5-HT\textsubscript{6} receptor illustrates an approach to AD treatment that differs significantly from the majority of AD research completed to date. Like the five medications currently available for treating AD, Lu AE58054 is intended to treat the symptoms associated with AD and is not expected to reverse the damage done by this disease.\textsuperscript{35}

**Previous Findings for Lu AE58054 Trials:**

**Phase 1:** No Phase I trials for Lu AE58054 are listed in publicly available databases.\textsuperscript{34}

**Phase 2:** A 24-week study indicated that the use of Lu AE58054 in combination with donepezil (10 mg/day) showed statistically significant improvement (p=0.004) in cognitive performance as measured by the Alzheimer’s Disease Assessment Scale Cognitive Subscale (ADAS-Cog). Other efficacy scales, including activities of daily living and measures of global status, also indicated positive trends for patients receiving Lu AE58054 and donepezil simultaneously.\textsuperscript{33}

**ACI-35 Vaccine**

ACI-35 is a vaccine currently being developed by a biotechnology company in Switzerland known as AC Immune. This study by AC Immune is the first AD vaccine study to ever take place. ACI-35 is an active vaccine that is intended to stimulate the immune system to
make antibodies against tau protein in order to prevent tau from causing neurofibrillary tangles within the brain. After recently obtaining $22 million from private investors, AC Immune began a Phase I clinical trial for the ACI-35 vaccine. An animal trial conducted in 2013 showed a significant reduction of phosphorylated tau in the brainstem and forebrain of ACI-35 vaccinated mice relative to placebo treated mice. In addition, this study showed a decrease in total insoluble tau levels in ACI-35 vaccinated mice. According to AC Immune, ACI-35 vaccine has an excellent safety profile due to its extremely specific antibody response and cell independent immune response.

**Solanezumab**

Solanezumab is an experimental AD drug created by Eli Lilly & Company that has the potential to delay the progression of AD. Solanezumab is a humanized monoclonal antibody that binds to beta-amyloid to prevent the formation of the insoluble beta-amyloid plaques that are often seen in AD patients. By binding to the soluble forms of beta-amyloid, Solanezumab allows individual proteins to be cleared before plaques begin to form. In a study conducted in 2002, a single injection of Solanezumab reversed memory deficits in mice despite the fact that the mice’s brain still contained previously formed amyloid plaques.

Although Eli Lilly & Company announced on August 24th, 2012 that both of its Phase III trials had failed to show significant improvement in patients with mild-to-moderate AD, the company made significant changes to their target population and began another Phase III trial in September 2013. The complete timeline of clinical trials for Solanezumab is shown in Figure 15.
For the latest trial, Eli Lilly & Company is enrolling patients with mild AD only, as more improvement was seen in these patients in the earlier Phase III trials. In addition, the company increased the trial population to 2,100 - an 800 subject increase from previous trials. Eli Lilly & Company also narrowed the trial population to patients that have evidence of brain beta-amyloid accumulation as detected by a PET scan or cerebrospinal fluid sample. According to the company, the previous Phase III trials may have failed due to the fact that approximately one-fourth of the previous participants did not have beta amyloid build up and were likely to have other types of non-AD dementia. Patients in the current Phase III trial will receive one 400 mg dose of Solanezumab intravenously each month for approximately 18 months. Due to an 18 month patient follow-up period, data from this study is not expected to become available until 2016.
MK-8931

MK-8931 is an experimental drug under development by Merck, an American pharmaceutical company. MK-8931 is an oral β-amloid precursor protein site-cleaving enzyme (BACE) inhibitor that is being evaluated for use in patients with mild to moderate AD. As a BACE inhibitor, MK-8931 decreases the production of β-amloid peptides by BACE. The goal of this inhibition is to limit the formation of β-amloid plaque deposits in the brain. According to Merck, the Phase I trial for MK-8931 showed that this drug can reduce the amount of β-amloid within the cerebrospinal fluid (CSF) of AD patients by more than 90 percent. The results of this trial also indicated that drug efficacy was dose-dependent, with the highest dose producing an average reduction of more than 80 percent compared to baseline levels of CSF β-amloid.

Merck is currently in the process of conducting a 78 week Phase II/III trial of MK-8931 known as EPOCH. The goal of this trial is to compare the efficacy of three different doses of MK-8931 (12, 40 and 60 mg) against placebo. In this trial, approximately 1,960 AD patients receive MK-8931 daily and the results of treatment are evaluated using ADCS-ADL and ADAS-Cog scores. After determining the safest and most effective dose of MK-8931, Merck plans to use a test population of approximately 1,500 patients for the main Phase III study. The complete timeline of clinical trials for MK-8931 can be seen in Figure 16.
Dihexa

Dihexa is an experimental drug that is currently being developed by Dr. Joseph Harding and Dr. John “Jay” Wright of Washington State University. Harding and Wright came across the earliest version of this drug in 1992 while studying the role of angiotensins in blood pressure regulation. After inadvertently isolating angiotensin IV, a peptide made of six amino acids, Harding and Wright noted that this molecule appeared to have an impact on the cognition levels of test animals. Because angiotensin IV was previously considered to be biologically inactive, Harding and Wright chose to focus their attention on this unique finding. After many years of research and numerous chemical modifications to the angiotensin IV molecule, Harding and Wright developed Dihexa.

Dihexa is orally active, metabolically stable, and has the ability to cross the blood-brain barrier. Together these characteristics make this compound extremely suitable for use as a prescription medication. In studies conducted by Harding and Wright, Dihexa has been shown to improve the cognitive function of aged rats based on the results of the Morris Water Maze test. This improvement in cognitive function is believed to be the result of Dihexa binding to
Hepatocyte Growth Factor (HGF), the primary growth factor that responds to damage within the nervous system, including neurodegenerative disease, brain injury, and spinal trauma. Normally two molecules of HGF must come together in order to create an active molecule that can readily bind to the c-Met receptor in the brain; however, Harding and Wright discovered that Dihexa has the ability to activate HGF by simply binding to it. Harding and Wright also discovered that HGF has an affinity for Dihexa that is one-hundred times greater than its affinity for another molecule of itself. Thus, Dihexa is extremely active even in very small doses.

The binding of Dihexa to HGF activates the molecule and allows it to bind to the c-Met receptor in the brain. This binding initiates a cascade of events that ultimately stimulate synaptogenesis, or the formation of new synapses in the brain. Although synaptogenesis naturally occurs in the brain, the use of Dihexa potentiates the activity of HGF and allows synaptogenesis to occur at much higher rates. Since AD is characterized by both a loss of neurons and synapses in the brain, Dihexa appears to have the ability to reverse the damage done by this disease.

Unlike the majority of AD studies that are currently taking place, the goal of Harding and Wright’s research is not to find the underlying cause of AD but to instead focus on fixing the damage done by this disease. Because HGF responds to all types of nervous system damage, Harding and Wright are also studying the effectiveness of Dihexa in the treatment Parkinson’s disease, Lou Gehrig’s disease (ALS), and multiple sclerosis (MS). Harding and Wright also emphasize that Dihexa’s estimated manufacturing cost is extremely low, meaning that it would be accessible to people of all socio-economic classes.
Despite the success of Dihexa in multiple “proof of concept” studies, there are still many obstacles that must be overcome before Dihexa can enter human trials. The main factor that is currently hindering Harding and Wright’s research is a lack of funding. Each animal trial for Dihexa is extremely expensive, with a single aged rat costing $630. Currently Harding and Wright are applying for a Small Business Innovation Research (SBIR) grant through the federal government. If their grant proposal is approved, Harding and Wright will use this funding to begin FDA-mandated trials in an independent laboratory. These trials would be used to confirm the effectiveness and safety of Dihexa and are estimated to cost $600,000-$700,000 (J Wright, Oral Communication, March 2014; J Harding, Oral Communication, March 2014).

Discussion

As illustrated in the previous sections, uncertainty about the true cause of AD has led to great diversity in the AD treatments that are currently under development. Although Lu AE58054 shows potential promise of reaching pharmacy shelves in 2017, this drug is not expected to revolutionize the way that AD is treated due to the fact that it cannot prevent or reverse the damage done by this disease. The majority of experimental drugs that show promise of revolutionizing the way that AD is treated, including Solanezumab, MK-8931 and the ACI-35 Vaccine, are focused on reducing the number of amyloid plaques and neurofibrillary tangles in the brain. Although these two factors were originally believed to be the main pathological causes of AD, some experts are beginning to think that amyloid plaques and neurofibrillary tangles are actually downstream effects of a larger problem. If proven to be true, this information could be detrimental to many AD drug trials. Although some researchers are attempting to fix the damage done by AD instead of preventing it, these drugs are a long
way from commercial availability. Dihexa, for example, is still in the earliest stages of drug development. Although there are hundreds of drugs currently under development, a major change in the way that AD is treated appears to be many years away.

**Conclusion**

AD is currently affecting millions of people worldwide, and this number is expected to climb drastically in the near future unless there is a breakthrough in AD treatment. Although five AD medications currently exist, the impact of these drugs on patient health is minimal at best. In order to truly combat AD and keep its prevalence from increasing three-fold in the next 36 years, a new medication that prevents or reverses the damage done by AD is desperately needed. Even though hundreds of AD drugs are currently under development, most are many years away from reaching the market. If we want to see a change in the way that AD is treated, then an increase in the funding for AD research is desperately needed. As actor Seth Rogen said at the U.S. Senate’s hearing on Alzheimer’s disease on February 26th, 2014: "Americans whisper the word Alzheimer's because their government whispers the word Alzheimer's. And although a whisper is better than the silence that the Alzheimer's community has been facing for decades, it's still not enough. It needs to be yelled and screamed to the point that it finally gets the attention and the funding that it deserves and needs."
Acknowledgements

I would like to express my sincere gratitude for my thesis advisor, Dr. Josh Neumiller. Over the course of my project he was extremely supportive, and his expertise in the field of pharmacy aided my work in numerous ways. I cannot thank him enough for taking time out of his busy schedule to assist me with this project. I would also like to thank Dr. Jay Wright and Dr. Joe Harding for providing me with invaluable information about their research. I learned so much from my interviews with them, and their help truly enhanced my thesis. In addition, I would like to thank Dr. Cathy Elstad for assisting me with my thesis from the very beginning. Her continual support and guidance helped me in more ways than I can describe. Finally, I would like to thank my family for all of their support throughout my academic career. I cannot thank them enough for all that they do for me.

Dedication

This thesis is dedicated to my grandparents, Jack and Loni Miller. Grandma, you’ve worked so hard to deal with this unfair disease, and I am so proud of you. Grandpa, I can’t thank you enough for all of the help and support you have given Grandma over the past few years. I love you both very much.
References Cited


Appendix

I. Last Observation Carried Forward (LOCF)

Last observation carried forward (LOCF) is a statistical method for dealing with missing data that results from patient drop out during a clinical trial. When LOCF analysis is employed, the last observed score for a patient who drops out of a study is recorded for all subsequent observation points.\(^{28}\)

II. Observed Case (OC)

Observed case (OC) is a statistical method for dealing with data sets that contain missing values. When OC analysis is employed, only patients who had an observation at the end-point visit are included in the statistical analysis.\(^{47}\)

III. ADCS-ADL Example Page\(^{47}\)

![Sample Case Report Form](image)

**ADCS – Activities of Daily Living Inventory**

Page 1 of 8

Information obtained through:  
☐ Informant visit  
☐ Telephone call

**Instructions:** For each question, use the subject’s name where (s) appears. Before beginning, read the questionnaire guidelines to the informant.

1. Regarding **eating:**
   Which best describes (s) usual performance during the past 4 weeks?
   - 3 ☐ ate without physical help, and used a knife
   - 2 ☐ used a fork or spoon, but not a knife, to eat
   - 1 ☐ used fingers to eat
   - 0 ☐ (s) usually or always was fed by someone else

2. Regarding **walking** (or getting around in a wheelchair), in the past 4 weeks, which best describes his/her optimal performance:
   - 3 ☐ mobile outside of home without physical help
   - 2 ☐ mobile across a room without physical help
   - 1 ☐ transferred from bed to chair without help
   - 0 ☐ required physical help to walk or transfer