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A cost-benefit analysis of Alzheimer’s disease treatment options

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Thesis

A COST-BENEFIT ANALYSIS OF ALZHEIMER'S DISEASE TREATMENT OPTIONS

by

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DEDICATION

I would like to dedicate this work to my late grandfather, Jose Ignacio, who is the reason my family is here today, and to my great-great-aunt, Julia Maria, who raised my grandmother before suffering with Alzheimer's disease.

ACKNOWLEDGMENTS

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A COST-BENEFIT ANALYSIS OF ALZHEIMER'S DISEASE TREATMENT OPTIONS

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ABSTRACT

Alzheimer's disease is a neurodegenerative disorder characterized by symptoms such as memory loss and behavioral change, and it is the sixth leading cause of death in the U.S. This literature-based thesis aims to detail the history of the disease as well as pertinent information, such as basic brain histology, disease pathogenesis, and genetic profiles of victims. The paper will then discuss the available treatment options, from their annual costs and mechanisms of action to an evaluation of their cost-effectiveness. The information in this paper was collected through an online investigation of sources including research studies and medical journals. The treatments discussed in this thesis consist of six drugs: aducanumab, donepezil, rivastigmine, galantamine, memantine, and memantine-donepezil combination. Aducanumab is the only disease-modifying drug to receive FDA approval, but its efficacy is marred in controversy and it lacks cost-effectiveness. The remaining five drugs all have similar cost-effective values, but generic donepezil is an outlier with significantly better results. This paper's findings indicate that generic donepezil is the most optimal treatment, but that further research should be conducted on aducanumab. Research also suggests that public health advocates must be vigorous in their attempts to make these drugs more affordable to the general population.

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ABBREVIATIONS

AA	amino acid
Aβ	β-amyloid
AD	Alzheimer's disease
APOE	apolipoprotein E
APP	β-amyloid precursor protein
ARIA	amyloid-related imaging abnormalities
BBB	blood-brain barrier
CI	cognitive impairment
CNS	central nervous system
Cybrid	cytoplasmic hybrid
EOAD	early-onset Alzheimer's disease
FAD	familial Alzheimer's disease
G1	Group 1
G2	Group 2
G3	Group 3
ICER	incremental cost-effectiveness ratio
IDE	insulin degrading enzyme
IgG1	human immunoglobulin gamma 1
LOAD	late-onset Alzheimer's disease
LRP	lipoprotein receptor-related protein
LTP	long-term potentiation

MCI	mild cognitive impairment
NIA	National Institute of Aging
NFT	neurofibrillary tangle
NMDA	N-methyl-D-aspartate
NT	neurotransmitter
PHF	paired helical filament
PIB	Pittsburgh Compound B
PS1	presenilin 1
PS2	presenilin 2
QALY	quality-adjusted life year
RAGE	receptor for advanced glycation end products
SOC	standard of care
WTP	willingness-to-pay

INTRODUCTION

To begin this thesis, the general characteristics of Alzheimer's disease will be reviewed including disease category, most common symptoms, and the subcategories of the disease. Furthermore, the relevant history and the most important discoveries pertaining to Alzheimer's disease will be detailed before revealing the objectives of this paper.

The Fundamentals of Alzheimer's Disease

Alzheimer's disease (AD), the most common cause of dementia and sixth leading cause of death in the U.S., is a chronic progressive neurodegenerative disorder characterized by memory loss, linguistic issues, psychological changes, and difficulties with the activities of daily life ("2020 Alzheimer's Disease Facts and Figures," 2020). Although rarely seen in people under the age of 50, this disease affects approximately 6% of the entire population of adults aged 65 and older, and its incidence increases in parallel with increased age (Burns & Iliffe, 2009; Rossor et al., 1984). AD is hallmarked by the accumulation of plaques in the brain and is always accompanied by symptoms that can be classified into three groups. Group 1 (G1) symptoms include issues with language, memory loss, and executive dysfunctions such as loss of planning skills and loss of some basic coordination. Group 2 (G2) is comprised of the psychological and behavioral changes such as depression, delusion, hallucination, and agitation. Group 3 (G3) symptoms deal with difficulties in daily life such as driving and shopping or basic tasks like eating and getting dressed (Burns & Iliffe, 2009).

This disease can be categorized as either early-onset (EOAD), familial (FAD), or late-onset (LOAD), and, although the difference between the three is still not entirely clear, it is believed that the early onset variety is much more severe in its effect and more widespread throughout the parts of the brain (Rossor et al., 1984). The early-onset variety of AD is categorized by its diagnosis prior to the age of 65, and there is recent evidence that only very few of these cases are the results of known mutations (Reitz et al., 2020). EOAD accounts for approximately 5%-10% of American AD cases, and has a reported prevalence of 24.2/100,000 people. That fraction increases as age increases between 45 and 64 years (Reitz et al., 2020). It is believed that, due to a lack of data, the cases that cannot be explained as the result of a known mutation, referred to as sporadic EOAD, actually have a higher prevalence than reported (Reitz et al., 2020).

FAD, which is the predominant subtype of EOAD, manifests itself relatively early but later on than EOAD. It is the result of an autosomal dominant inheritance pattern that is based around mutations in any of three genes (Dewji & Singer, 1996). In other words, FAD accounts for the cases of EOAD that can be explained by known mutations. The most well understood of those genes involves point mutations affecting the gene coding for β-amyloid precursor protein (APP) on chromosome 21. The other two involve mutations on chromosomes 1 and 14 coding for presenilin 2 (PS2) and presenilin 1 (PS1), respectively (Dewji & Singer, 1996). Both of those genes code for integral

transmembrane proteins that are 67% homologous with each other, and all three of these mutations lead to the acceleration of the process of accumulating β-amyloid (Aβ) plaques (Dewji & Singer, 1996). Despite only three genes to target, there is no cure for FAD, but there are a variety of treatments that will be discussed.

In contrast to EOAD and FAD, there is a better understanding of LOAD due to the substantial amount of data regarding its prevalence. AD cases fall into this category if incidence occurs after the age of 65 (Reitz et al., 2020). Unlike FAD's strong link to three inherited genes, LOAD is estimated to have heritability in only between 60% and 80% of cases and all of them share the same one gene in common which is apolipoprotein E (APOE) on chromosome 19 (Rabinovici, 2019). APOE encodes an important cholesterol transporter in the brain and it appears as three different alleles, which will be covered in detail later, but the importance of this is that only one of those alleles increases the risk of AD while the others guard against it. However, this is merely a risk factor because the genetics of LOAD are not yet entirely understood (Rabinovici, 2019).

Table 1: Comparison of the Basic Characteristics of EOAD and LOAD
Taken from (Agrawal, 2021).

Type of AD	**Early-Onset**	**Late-Onset**
Onset Age	< 65 years old	> 65 years old
% of AD	5% - 10%	90% - 95%
Genetic Profile	PS1, PS2, APP	APOE

Major Discoveries Relating to Alzheimer's Disease

In early 1901, the husband of 50-year-old Auguste Deter noticed that she became overwhelmingly paranoid then quickly digressed into sleeping disorders, memory loss, aggression, mood swings, and confusion. Later that year, she was admitted to Frankfurt Psychiatric Hospital where she was observed by Alois Alzheimer. Auguste passed away in that same hospital in 1906, so Alzheimer was able to study her brain both histologically and morphologically (Hippius & Neundörfer, 2003).

Initially, Alzheimer had diagnosed Auguste with presenile dementia although he knew there was something different. However, in the years in between Auguste's admittance to this hospital and eventual death, Alzheimer would leave Frankfurt to work closely with Franz Nissl and Emil Kraepelin (Yang et al., 2016). Together, they found neurofibrillary tangles (NFTs) and amyloid plaques were both present in the brain, and they determined that the unexplainable symptoms were caused by the thinning and deterioration of the cerebral cortex (Yang et al., 2016). Those findings, in conjunction with Alzheimer's four years of observations and encouragement from Kraepelin, would lead the disease to be named after Alzheimer and became the basis of his first lecture on this form of cognitive impairment (CI) (Hippius & Neundörfer, 2003; Yang et al., 2016).

Table 2: Timeline of Major Discoveries Relating to AD
This table presents the most relevant discoveries and events relating to AD and the treatment of it. Taken from (*Milestones*, n.d.).

1906	Alois Alzheimer completes his study of Auguste Deter, who would become the first patient to be diagnosed with Alzheimer's disease and laid the groundwork for future research.
1931	The invention of the electron microscope allows researchers to study brain cells in far greater detail.
1968	The development of cognitive measurement scales allows researchers to correlate measured CI with estimates of number of brain lesions.
1974	The founding of the National Institute of Aging (NIA) creates a federal agency to support Alzheimer's disease research.
1984	George Glenner and Cai'ne Wong discover the Aβ protein, which is a major component of brain plaques.
1986	Researchers discover the tau protein, which is a major component of NFTs.
1987	Researchers identify the APP gene on chromosome 21 as the first deterministic gene associated with rare forms of inherited Alzheimer's disease.
1993	Researchers identify APOE-e4 on chromosome 19 as the first major risk factor gene associated with AD.
1993	Cognex become the first drug approved by the FDA for the treatment of AD. Four more drugs would be approved over the next ten years.
2004	Researchers make their first report about Pittsburgh Compound B (PIB) which attaches to plaques and serves as an imaging tool in PET scans.

2010	Researchers publish a model relating Alzheimer's biomarkers to disease stages and symptom severity. This model has become a focal point in Alzheimer's biomarker research
2013	Researchers from around the world collaborate to create a genomic analysis relating to AD. They discover 20 genetic variations linked to AD, of which 11 had not previously been linked to the disease.
2014	Researchers from Rush University find that the number of annual deaths from AD is much higher than the number reported.
2018	The Alzheimer's Association releases the Dementia Care Practice Recommendations to help healthcare professionals deliver the best care possible to dementia patients.
2021	Aducanumab receives approval from the FDA as a treatment for Alzheimer's disease. This is the first treatment to address the biology of AD.

Specific Aims

This paper will provide the relevant background information about the histology and physiology of the brain as it relates to AD, as well as the typical pathogenesis, clinical presentation, and complete genetic profiles and patterns of inheritance of the disease. Then, the currently approved treatment options will be explored and detailed before a discussion in the form of a cost-benefit analysis based on the physical and financial implications of each treatment versus its clinical outcomes.

AFFECTED BRAIN CELLS

In order to fully understand the pathogenesis of AD, one must first grasp the basics of the brain cells that are affected by the plaques and NFTs that form. This section of the paper will deliver that information along with graphics to gain an understanding of these cells.

Neurons

The general belief is that there are about 100 billion neurons in the human brain, which is an unfathomable number. The job of the neuron is simple: relay messages back and forth between brain and body. Neurons are often subdivided into parasympathetic or sympathetic based on their function and their relative neurotransmitter (NT) (Garman, 2011). Each neuron is composed of dendrites, a cell body, an axon, and the axon terminals. The dendrites receive signals while the axon specializes in moving the signal along the neuron, and the axon terminals meet with the dendrites of the next relevant neurons (Garman, 2011).

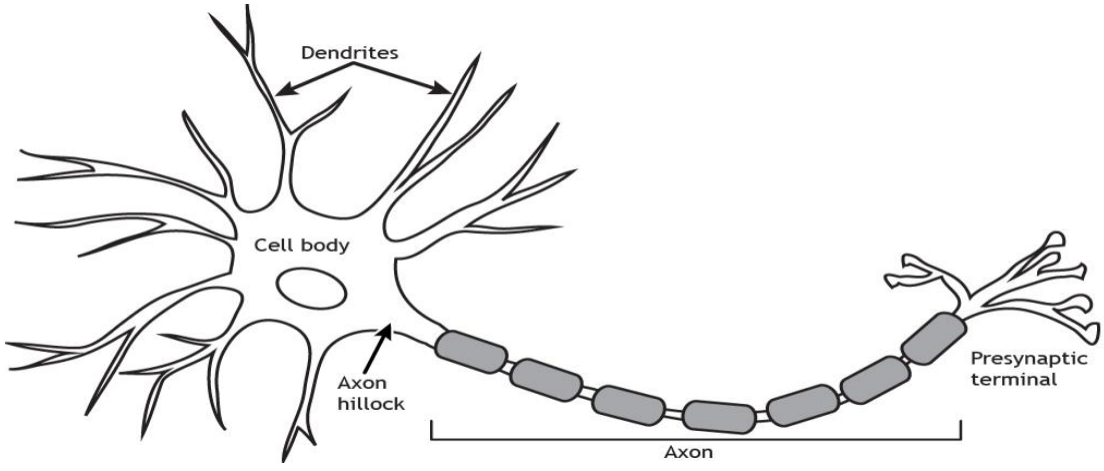

Figure 1: Basic Structure of a Neuron
Taken from (Henley, 2021).

Microglia

The other cell types that are often implicated in AD are the glial cells, and among those the microglia are most relevant. These cells make up the reticuloendothelial system of the central nervous system (CNS) and they account for 5% to 20% of the total glial cell population, which is estimated to be larger than the population of neurons. Microglia are generally heterochromatic with elongated nuclei, and they are often found in close proximity to lesions of neuronal degeneration (Garman, 2011). Functionally, the network of microglia forms a significant part of the immune system of the CNS due to their phagocytic behavior. They are highly plastic in their function while maintaining a low threshold for activation and responding rapidly to either direct or indirect threats to the CNS (Graeber, 2010).

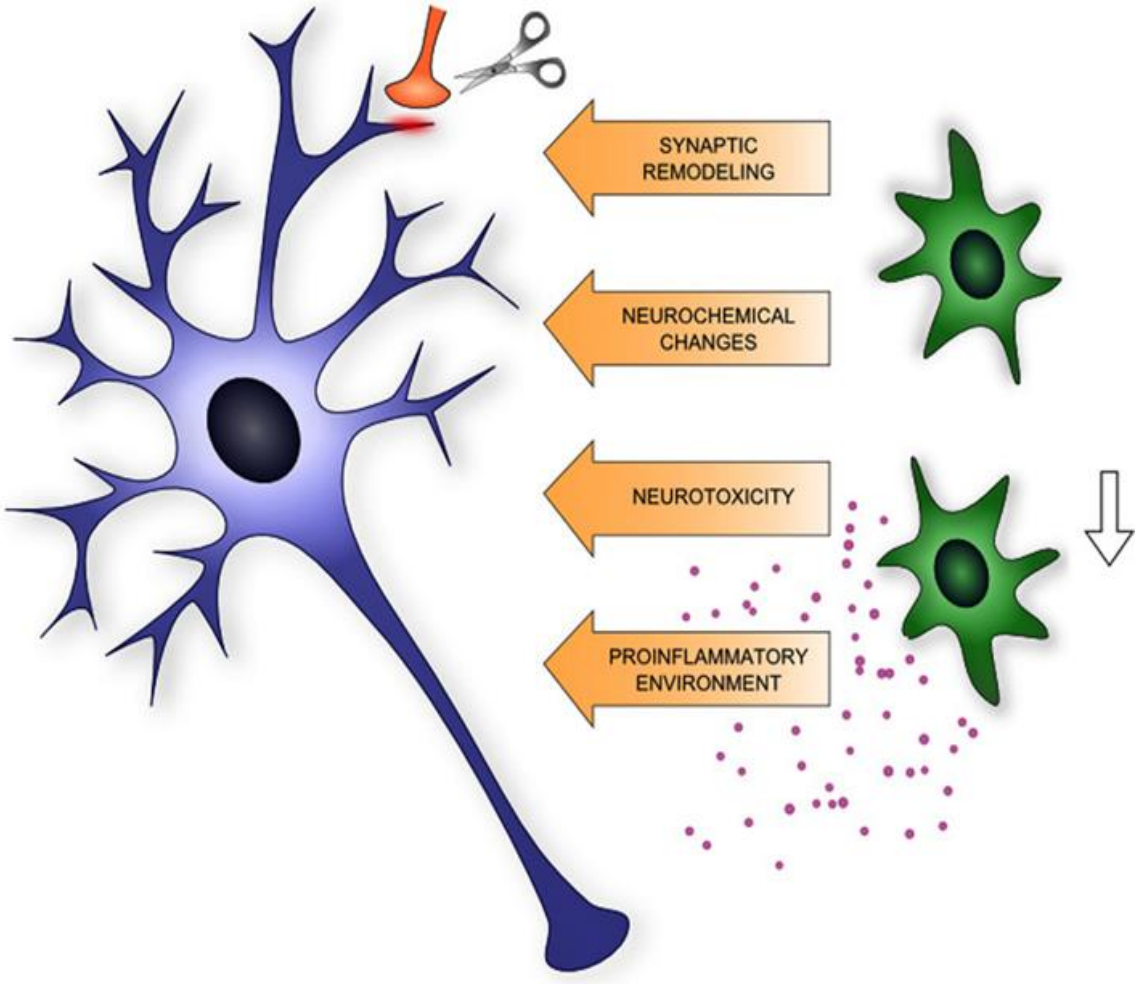

Figure 2: Basic Effects of Microglia on Neurons in CNS
This figure shows the basic effects that the network of microglia can impart on the neurons of the CNS. It also serves to demonstrate some of the plasticity displayed by the microglia. Taken from (Kovacs, 2012).

Astrocytes

Similar to the microglia, astrocytes play a pivotal role in the development and advancement of AD due to their roles as effector cells whereas they can either slow the progression by functioning properly or accelerate it by failing to perform their neuroprotective tasks (Dzamba et al., 2016). However, astrocytes

can be differentiated from the microglia by their intimate relationship with neuronal synapses as they help maintain the blood-brain barrier (BBB). Often times, the astrocytes are even found completely entangled with or wrapped around various types of synapses (Papouin et al., 2017). The importance of this relationship is that, in many cases, the astrocytes must first be affected by NTs before the neurons can function properly. These cells will sense a change in NT concentration and react accordingly whether that be a gain or loss of function via changes in their behavioral state (Papouin et al., 2017).

Oligodendrocytes

Unlike the microglia and the astrocytes, the oligodendrocytes have a role in the CNS that is far easier to understand. These cells form the myelin sheath that encapsulates the neurons of the CNS, which is essential for the rapid signaling and extensive computational ability present in the brain (Butt et al., 2019). Oligodendrocytes and their product, myelin, also serve to deliver nutritional support for neuronal axons. Even though the brain has a fantastic ability to regenerate oligodendrocytes, the degeneration of these cells and their myelin results in axonal failures and general neuronal death and is one of the early hallmarks of potential AD (Butt et al., 2019).

ALZHEIMER'S DISEASE

Now that the fundamentals and history of AD have been covered as well as a quick review of the most pertinent brain cells, this paper can move on to the more strenuous details of AD. This section will detail things like the symptoms and the genetics of AD before taking a deep dive into the most essential hallmarks of the disease: amyloid plaques and neurofibrillary tangles.

General Symptoms

As previously mentioned, the symptoms of AD can be divided into three primary groups: G1 symptoms are executive dysfunctions, G2 symptoms are behavioral and psychological changes, and G3 symptoms cover difficulties with daily tasks (Burns & Iliffe, 2009). Executive functions, as they relate to G1 symptoms, are often referred to as working memory, inhibition, set shifting, and fluency. Those groups of functions all work together to create the structure required for more complex cognitive functioning (Rabinovici et al., 2015). Since executive functions rely on the prefrontal and parietal cortexes as well as the thalamus, cerebellum, and basal ganglia, G1 symptoms can arise from injury to any of those regions of the brain (Rabinovici et al., 2015). Behavioral and psychological changes, also known as neuropsychiatric symptoms, are non-cognitive symptoms, but they are just as clinically important as the rest as they appear in 90% of dementia case (Cerejeira et al., 2012). They include feelings like agitation, anxiety, elation, irritability, and depression as well as other things like changes to sleep or appetite, hallucinations, and atypical motor function. The

reason for development of these symptoms is still unclear but it is certain that they are a major diagnostic marker of dementia diseases (Cerejeira et al., 2012). G3 symptoms represent the final stage of AD and are the culmination of all the symptoms that manifested earlier on. At this point, the patient is effectively incapable of taking care of themself (Bauer & Shea, 1986).

Figure 3: Visualization of AD Symptoms
Taken from (*What Is Alzheimer's Disease?* | *Columbia* | *Center of Excellence in Alzheimer's Disease*, n.d.).

Genetics and Inheritance

Although increasing age has been identified as the most significant risk factor for developing AD, there are still four genes, one of which that is a risk factor and three of which that are causative, that are known to be prevalent in AD progression (Bekris et al., 2010). As stated earlier, the majority of EOAD cases are not caused by known mutations and, therefore, those cases render no information regarding genetics or inheritance patterns even though 60% of cases have affected relatives (Bekris et al., 2010; Reitz et al., 2020). However, the subtype of EOAD known as FAD is directly linked to the three causative genes which all display autosomal dominant inheritance patterns: PS1, PS2, and APP (Bekris et al., 2010; Dewji & Singer, 1996). The next few paragraphs will give some important details each of these genes.

The first of the aforementioned genes, PS1, is found on chromosome 14 and codes for a multi-spanning transmembrane protein (Sherrington et al., 1995). There are 176 known mutations of this gene associated with AD, which accounts for between 18% and 50% of FAD cases (Theuns et al., 2000). The presenilin protein class is a significant part of the protease complex that cleaves the γ-secretase of APP. Any mutation causing a lack of function of this protein will increase the ratio of Aβ42 to Aβ40 and, therefore, reduce γ-secretase activity (Bekris et al., 2010). The cases associated with these PS1 defects are often the most severe AD cases, and can lead to diagnoses sometimes as early as 30 years of age (Bekris et al., 2010).

In 1995, a gene highly homologous to PS1 was discovered on chromosome 1 and was later named PS2 (Levy-Lahad et al., 1995). Relative to PS1's vast array of mutations, defects on PS2 were found to be very sparse and presented with different clinical outcomes. The age of onset among patients with PS2 mutations was much older and far more variable than those with PS1 defects (Bekris et al., 2010), which has led researchers to believe that these mutations have a lower degree of penetrance and require more outside factors (Tandon & Fraser, 2002). The PS2 protein functions very similarly to the PS1 protein and a lack of function leads to the same issues as were discussed above (Citron et al., 1997; Scheuner et al., 1996).

Since it was first discovered that the Aβ peptide was the proteolytic product of the APP membrane glycoprotein (Kang et al., 1987), there have been 32 possible missense mutations found on the APP gene on chromosome 21. The majority of them are found at secretase cleavage sites (Bekris et al., 2010), and increase the chances of developing plaques by increasing the level of Aβ42 and decreasing the level of Aβ40 (Scheuner et al., 1996). These mutations are often not seen in sporadic cases, but they account for approximately 10%-15% of FAD cases (Bird, 2008). In general, cases involving an APP mutation will have an age of onset on the early side of the range in the mid-40s through the 50s (Bekris et al., 2010). Because APP is located on chromosome 21, there is a strong link between AD and Down Syndrome, or trisomy 21, due to the overexpression of APP in Down Syndrome (Mapstone et al., 2020).

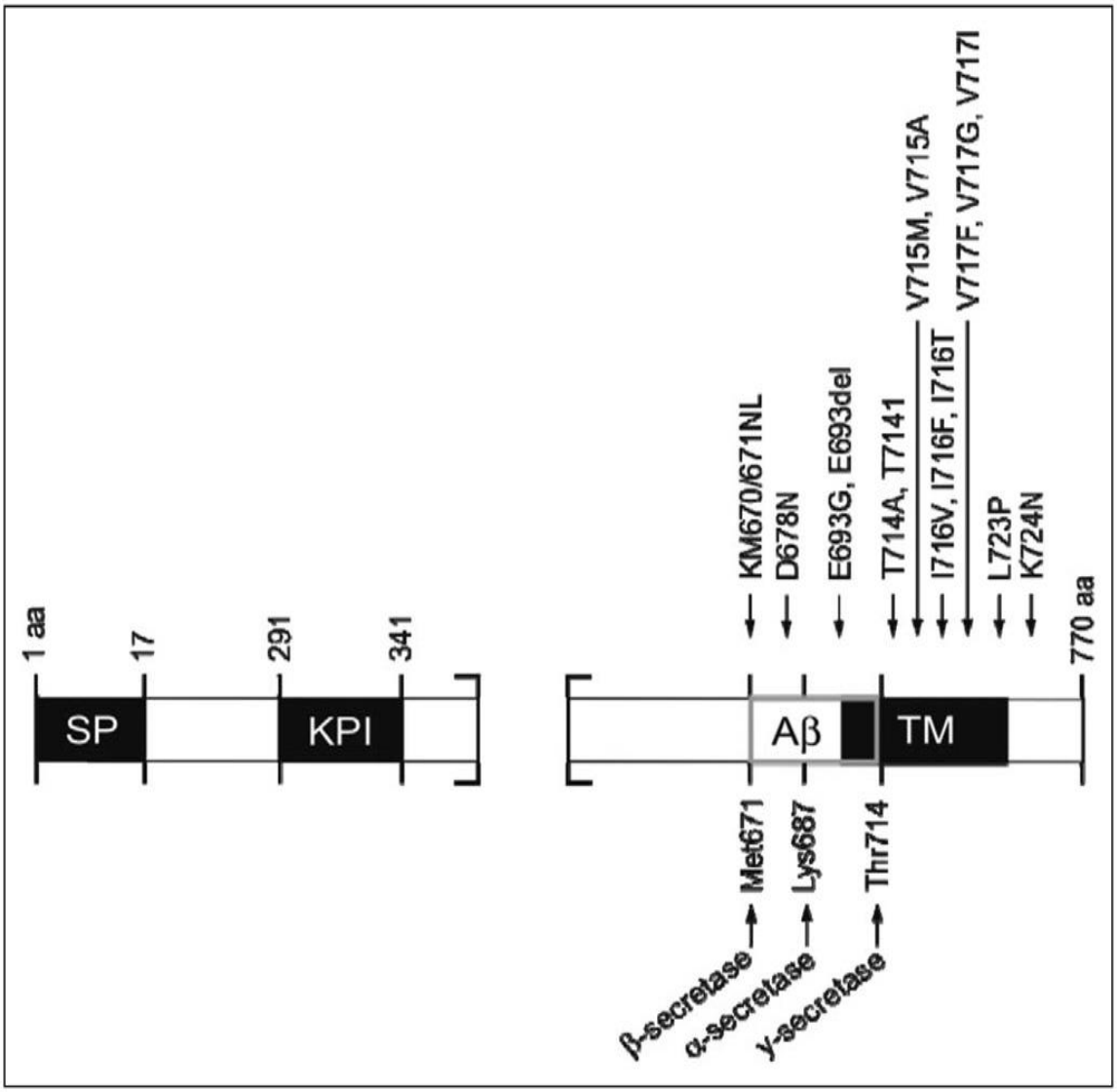

Figure 4: APP Structure and Potential Mutations
The mutations shown above are the most prevalent of the 32 that can occur on the APP gene. The danger of these mutations is that they can cause and accelerate the development of amyloid plaques in the brain. Taken from (Bekris et al., 2010).

Despite all three of those FAD-causative genes displaying autosomal dominant inheritance, they jointly account for under 1% of all AD cases. On the other hand, sporadic LOAD accounts for about 90% of cases (Bekris et al.,

2010). Although there is no known causative gene, mutations of the APOE gene have been consistently found to be risk factors of LOAD. However, many carriers of such mutations live into their 90s without AD which suggests other factors play a role in LOAD (Bekris et al., 2010). There are three possible alleles of the APOE gene: e2, e3, and e4. In studies, it has been found that control groups frequently possess either e2 or e3 and that groups known to have AD frequently carry the e4 allele (Bekris et al., 2010). It has also been found that individuals that are homozygous for e4 alleles are at greater risk than heterozygous individuals (Chai, 2007). These carriers of e4 have been found to have higher LDL cholesterol, increased mitochondrial damage, and are more likely to develop plaques and tangles (Bekris et al., 2010; Gibson et al., 2000; Z. Nagy et al., 1995).

Table 3: Summary of Genes Known to be Associated with AD
Taken from (Bekris et al., 2010).

Gene Abbreviation	Gene Name	Chromosome	Inheritance
APP	Amyloid precursor protein	21	Autosomal Dominant
APOE	Apolipoprotein E	19	Sporadic
PS1	Presenilin 1	14	Autosomal Dominant
PS2	Presenilin 2	1	Autosomal Dominant

Amyloid Plaques and Neurofibrillary Tangles

Throughout this paper, there has been frequent mention of amyloid plaques and NFTs, and this section will dive into deeper detail on both of those things. First, there a few essential facts that should be known. Amyloid plaques are extracellular and are the result of Aβ peptide deposition. NFTs are intraneuronal and are caused by the binding and ensuing buildup of tau proteins. Lastly, Aβ and tau form and accumulate entirely separately but their soluble forms may have amplifying effects on one another (Bloom, 2014).

In short, an amyloid plaque is created via the accumulation of Aβ42 monomers first into toxic oligomers and then into the plaque itself, and fortunately there exists a good understanding of that process. The key players in this metabolic process are two membrane-bound endoproteases, β- and γ-secretase, which sequentially cleave the APP glycoprotein (Murphy & LeVine, 2010). β-secretase cleavage results in the secretion of the sAPPβ derivative and a remaining 99 amino acid (AA) fragment, which is then cleaved by γ-secretase resulting in Aβ monomers. However, the γ-secretase cleaving can result in monomers of different C-terminal positions. The most common forms are Aβ40 and Aβ42 appearing at about 80%-90% and 5%-10%, respectively (Murphy & LeVine, 2010). The form Aβ42, which is longer and more hydrophobic, is the fibrillogenic form and is seen far more often in NFTs (Selkoe, 2001). In EOAD cases, it is common for the genetic mutations previously discussed to result in an

increase in Aβ42 monomers resulting from γ-secretase activity which, in turn, leads to increase amyloid plaque formation (Scheuner et al., 1996; Suzuki et al., 1994). In a normally functioning brain, there is a substantial amount of effort put into the degradation or removal of undegraded monomers. There are two mechanisms of removal: lipoprotein receptor-related protein (LRP) on the brain side of the BBB and by the receptor for advanced glycation end products (RAGE) on the blood side of the BBB (Deane et al., 2003; Shibata et al., 2000). If those mechanisms are interfered with, the result is another method by which Aβ42 monomers can accumulate in the brain and eventually form amyloid plaques (Van Uden et al., 2002).

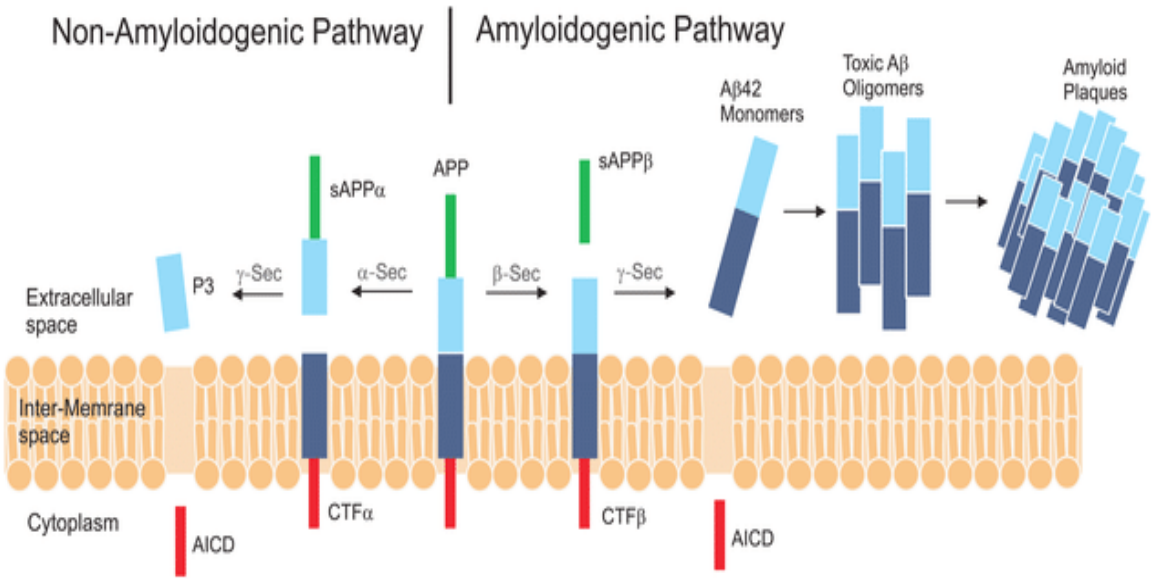

Figure 5: Pathway from APP to Amyloid Plaque
The amyloidogenic pathway is the result of sequential β-secretase and γ-secretase cleavage. The result is the secretion of an sAPPβ derivative and the creation of an Aβ42 monomer, which then associates with other monomers and eventually becomes an amyloid plaque. Taken from (Bachurin et al., 2017).

Whereas the process of developing amyloid plaques is a bit complex, the development of NFTs is fairly straightforward. Tau is a neuronal microtubule-associated phosphoprotein that is encoded by the MAPT gene on chromosome 17. Normally, unphosphorylated tau functions by binding to and stabilizing microtubules, but phosphorylation can occur at about 71 possible sites by any of 20 or more protein kinases and render tau nonfunctional (Beharry et al., 2014). GSK-3 is the most relevant of the kinases because it can act on different sites of the tau protein to create NFTs or generate Aβ (Corbo & Alonso, 2011). To counter the kinases, phosphatases, such as PP-2A and PTEN, are charged with the dephosphorylation of tau (Beharry et al., 2014). PP-2A accounts for 70% of tau phosphatase activity in the human brain, is regulated by endogenous protein inhibitors, and can regulate GSK-3 activity (Liu et al., 2004; Qian et al., 2010).

The mechanism leading to hyperphosphorylation of tau is not yet well understood, but there are many possible ways for it to occur (Beharry et al., 2014). However, the gist of it is that is that hyperphosphorylated tau monomers will join to form, in increasing size, dimers, soluble oligomers, paired helical filaments (PHFs), and they will eventually form NFTs. Somewhere in the pathway, there is also the possibility that granular tau oligomers (GTOs) are formed instead of or after the oligomers (Cowan & Mudher, 2013). Either way, the end result of the hyperphosphorylation of tau is the development and deposition of NFTs.

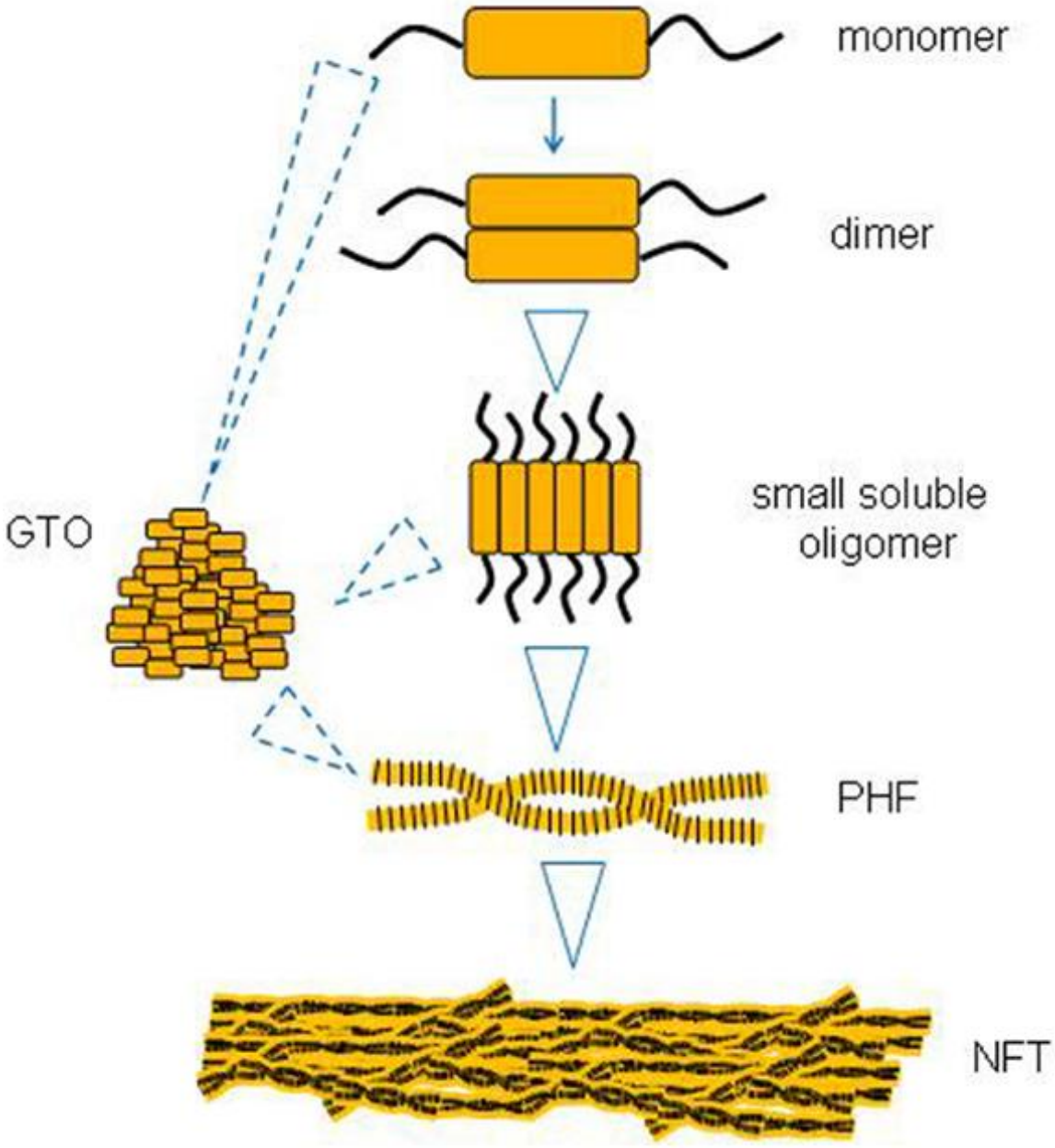

Figure 6: Simple NFT Formation from Tau Protein
Taken from (Cowan & Mudher, 2013).

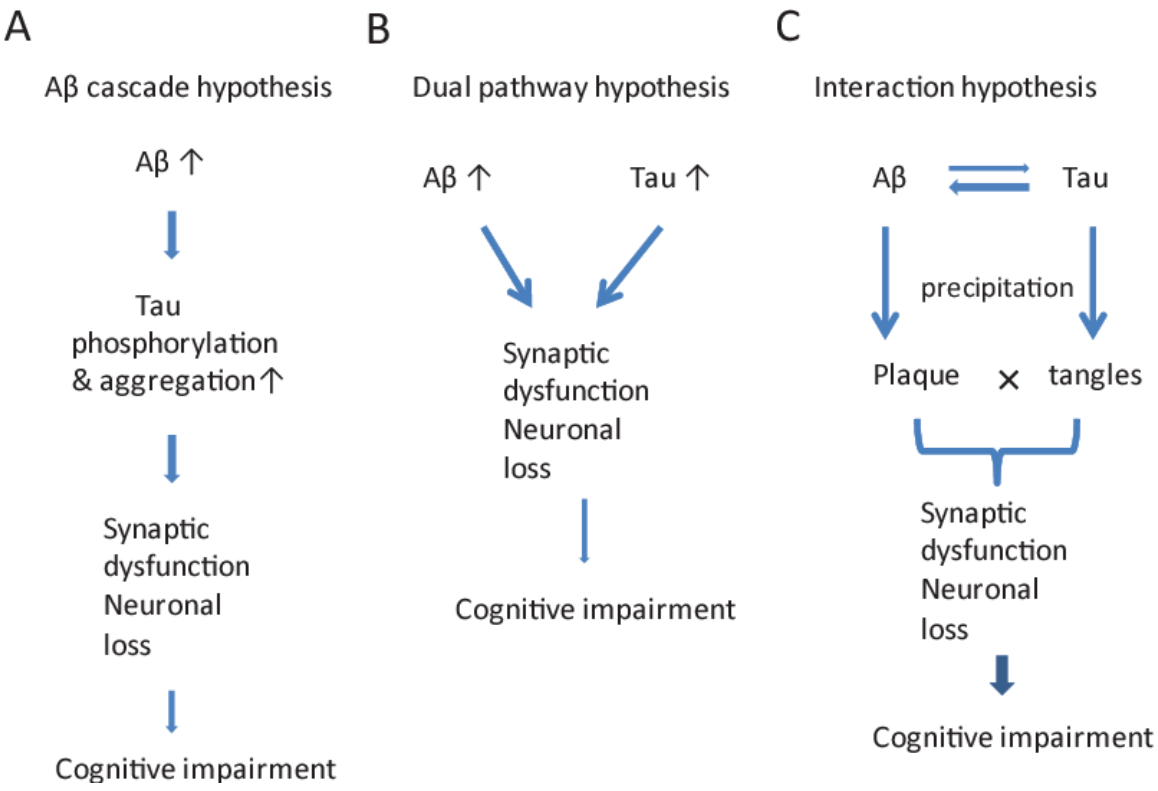

Figure 7: Hypothesized Pathogenic Relationships Between Aβ and Tau
(A): it is believed that an increase of Aβ leads to an increase of tau aggregation and thus neuronal loss and CI. (B): increases in Aβ and tau simultaneously leading to CI. (C): Aβ and tau stimulate each other into separately developing plaques and tangles that cause CI. Taken from (Han & Shi, 2016).

Pathogenesis Hypotheses

Given the material discussed previously in this section, this paper can now dive into the two most well-studied AD pathogenesis hypotheses. Since Alois Alzheimer's time, there has been an ongoing debate regarding whether AD represents a primary or secondary amyloidosis. Alzheimer himself believed the histopathology to be a secondary process, and yet there has been research suggesting clear instances of a primary amyloidosis in AD cases (Davis &

Chisholm, 1999; Scheuner et al., 1996). This debate is at the center of the discussion on AD pathogenesis, and pits the amyloid cascade hypothesis versus the mitochondrial cascade hypothesis.

The amyloid cascade hypothesis assumes that AD progression always involves a primary amyloidosis (Swerdlow, 2007a). As previously discussed, such an amyloidosis can be caused by genetic mutations in at least one of three genes: PS1, PS2, and APP (Goate et al., 1991; Levy-Lahad et al., 1995; Sherrington et al., 1995). In normal functioning, APP can either be processed by a combination of either α-secretase, which cuts APP 83 AAs from the C-terminal, then γ-secretase or β-secretase, which cuts APP 99 AAs from the C-terminal, then γ-secretase. There are two cuts in both process from γ-secretase, which is mediated by PS1 and PS2 (Swerdlow, 2007a). In the α-secretase scenario, the result is sAPPα and P3, and there is no chance for amyloidosis. The β-secretase scenario results in sAPPβ and a small C-terminal fragment known as CTFβ. When CTFβ is cut by γ-secretase, it results in a 4 kD peptide that is the Aβ peptide in varying lengths of 38-43 AAs (Swerdlow, 2007a).

When those genetic mutations do occur, they lead to an increase in the production of toxic Aβ42 and, simultaneously, a decreased production of the common Aβ40 (Scheuner et al., 1996). Furthermore, in contrast to the early versions of this hypothesis, it has come to be believed that the most toxic Aβ42 is actually the portion that is not part of the plaques and, instead, is a freely floating fragment (Lesné & Kotilinek, 2005). This pathogenic hypothesis is best

representative of the EOAD cases with autosomal dominant inheritance, also known as FAD, and this cannot be shown to also be the case for LOAD cases because the genetic implications of such cases are not well understood (Swerdlow, 2007a). The degradation of Aβ is done enzymatically by enzymes like neprilysin and insulin degrading enzyme (IDE). In non-FAD cases of AD, increased Aβ production is associated with IDE downregulation suggesting an upstream event which would cause the pathogenesis to be a secondary amyloidosis (Cook et al., 2003; Swerdlow, 2007a).

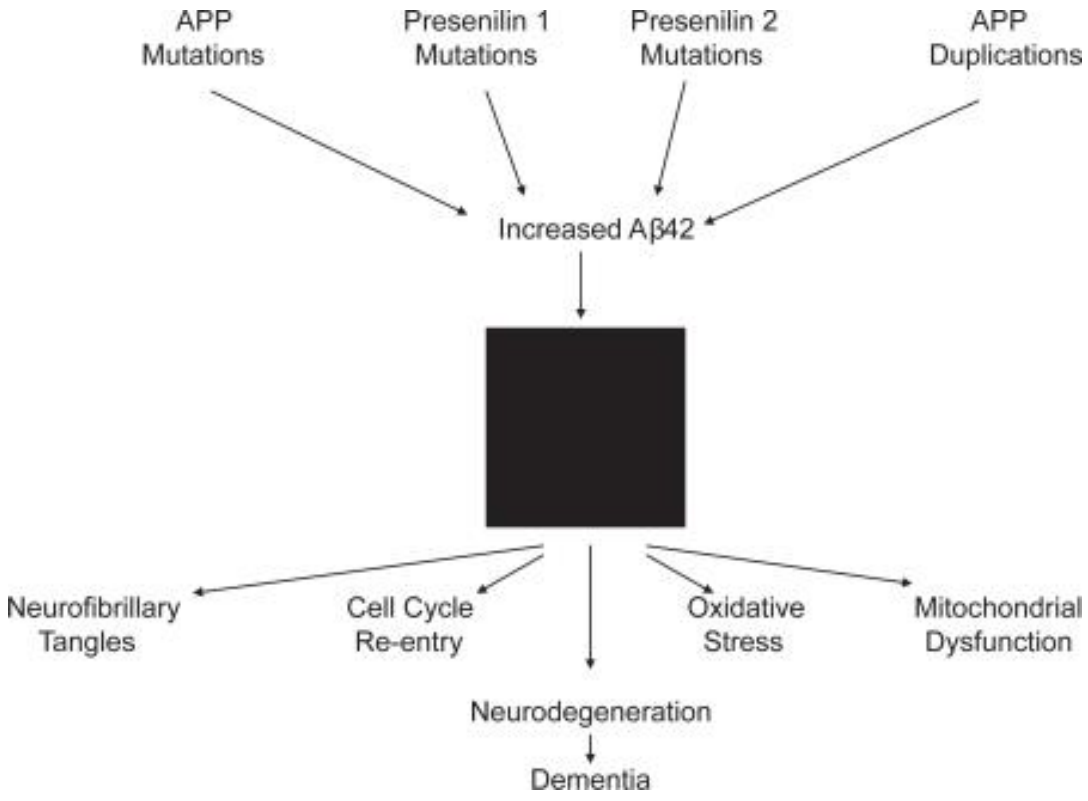

Figure 8: Amyloid Cascade Hypothesis
In this hypothesis, amyloidosis is the primary process in AD pathogenesis. It is the direct result of mutations in PS1, PS2, or APP. The black box represents the not well understood mechanisms by which amyloidosis leads to AD. Taken from (Swerdlow, 2007a).

In contrast to the amyloid cascade hypothesis and in agreement with Alois Alzheimer, the mitochondrial cascade hypothesis assumes that AD is caused by a secondary amyloidosis (Swerdlow, 2007a). This hypothesis can be summarized by a few assumptions and assertions. Firstly, it assumes that AD and brain aging have similar mechanisms physiologically, and that mitochondrial dysfunction cannot be a consequence of neurodegeneration because it is systemic. This hypothesis posits that non-Mendelian genetic factors lead to LOAD cases, and that mitochondrial dysfunction in the brain is the force behind amyloidosis, tau phosphorylation, and cell cycle reentry (Swerdlow & Khan, 2004). In AD cases, dysfunction is seen in brain, platelet, and fibroblast mitochondria in addition to defects in three mitochondrial enzymes: pyruvate dehydrogenase, alpha ketoglutarate dehydrogenase, and cytochrome oxidase (Gibson et al., 1998; Swerdlow, 2002). The amount of cytochrome oxidase in AD brains has been found to be normal but the structure or the enzyme appears to be altered (Parker & Parks, 1995). Cytoplasmic hybrid (cybrid) studies have shown that mtDNA can also account for the reduced cytochrome oxidase activity (Swerdlow, 2007b). These factors lead to oxidative stress, which is one of the various mechanisms that cause mitochondrial dysfunction in neurodegenerative diseases (Ding et al., 2006).

Furthermore, AD cybrids have been found to overproduce Aβ42 if they have decreased activity of cytochrome oxidase and that sodium azide, a cytochrome oxidase inhibitor, will force APP processing towards the

amyloidogenic pathway and increase tau phosphorylation (Gabuzda et al., 1994; Khan et al., 2000; Szabados et al., 2004). There also exists a reciprocal relationship between Aβ and cytochrome oxidase because Aβ itself specifically inhibits the activity of cytochrome oxidase (Crouch et al., 2005; Devi et al., 2006). As seen in Figure 9, this creates a loop where mitochondrial dysfunction causes a secondary amyloidosis and, in turn, the amyloidosis causes neurodegeneration as well as more mitochondrial dysfunction.

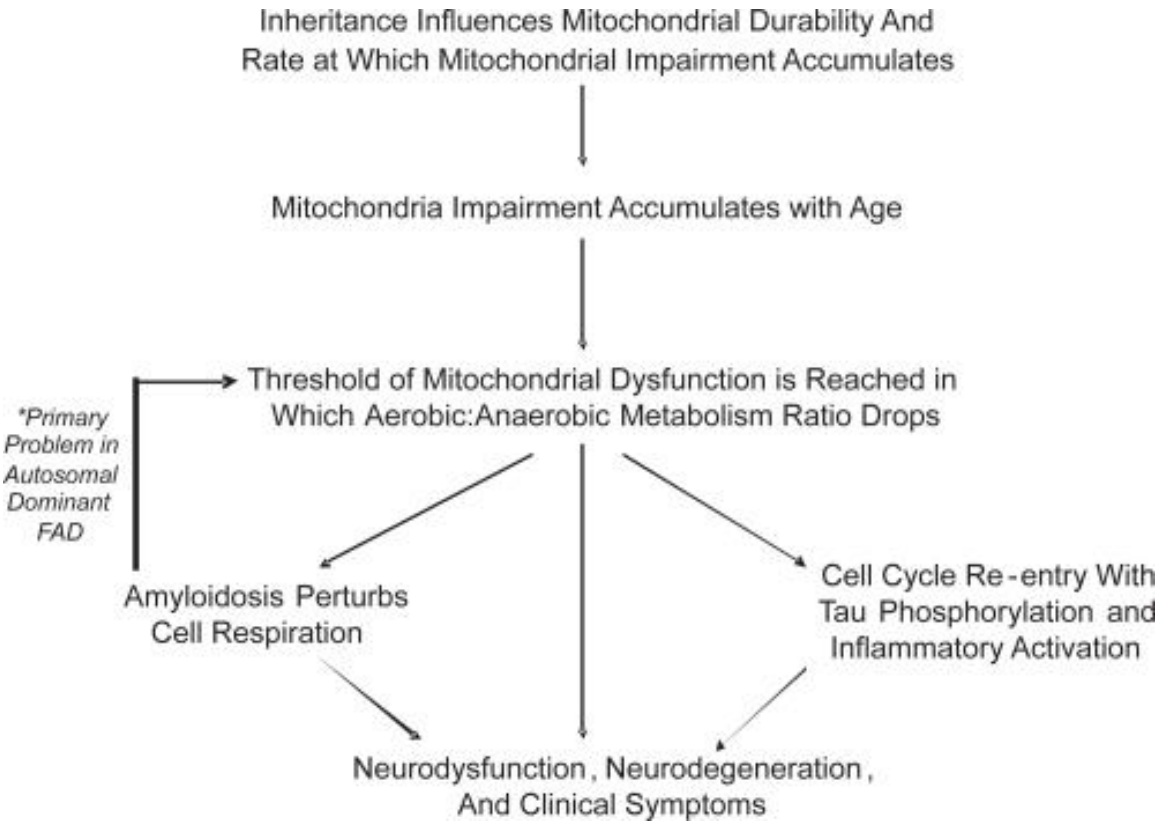

Figure 9: Mitochondrial Cascade Hypothesis
Taken from (Swerdlow, 2007a).

TREATMENT OPTIONS

After covering the contents of the three previous three sections, there is now have a good understanding of the history, fundamentals, and pathogenesis of AD. This coming section will now seek to build off of all the information discussed thus far as it describes the current treatment options for AD. That will include financial and physical implications in addition to the mechanisms and efficacies of the treatments. Overall, reported AD deaths increased 146% between 2000 and 2018, and, currently it is estimated that $355 billion are spent per year on caring for patients with AD but that total is expected to reach $1.1 trillion by the year 2050 (Franklin, 2021).

Aducanumab

On June 7th 2021, the FDA, through an 'accelerated approval pathway,' approved the sixth and most recent treatment for AD: aducanumab sold as Aduhelm by Biogen (Commissioner, 2021; J. L. Cummings et al., 2019). Because aducanumab's approval was accelerated, it is implied that this drug has a significant clinical advantage over the other five existing therapies or that it has a clinically beneficial impact on a specific biomarker. Aduhelm also had a 'Fast Track' designation, which implies that evidence relating to the drug's efficacy has shown that it has potential to affect a previously unaddressed medical need. This was the first newly approved AD treatment since 2003 and the first one to be considered disease-modifying (Commissioner, 2021). The prescribing information for Aduhelm was updated to clarify that mild CI and the mild

dementia stage of AD are the approved indicators for use (Franklin, 2021). Aducanumab is administered intravenously throughout at least 7 successive hourlong infusions all increasing in dosage and separated by 3-4 weeks (Schneider, 2020). The current yearly cost of Aduhelm is $28,200 even though it was originally priced at $56,000 (*After Criticisms, Biogen Slashes Price of Its Alzheimer Drug in Half*, 2021).

Aducanumab is classified as a human immunoglobulin gamma 1 (IgG1) monoclonal antibody, and it works by crossing the BBB and, with specificity, binding Aβ in both their soluble oligomer and insoluble fibril forms (Kastanenka et al., 2016; Sevigny et al., 2016). More specifically, the mechanism of action of aducanumab is binding to a linear epitope formed by 3-7 Aβ AAs (Arndt et al., 2018). This results in increased selectivity for aggregated forms of Aβ thus resulting in decreased Aβ plaques and sometimes even reduced tau phosphorylation (J. Cummings et al., 2021; Sevigny et al., 2016). Unfortunately, the efficacy of the drug is up for debate as some researchers condemn its approval and other suggest it was rightfully approved. To summarize, there were two major studies done by the FDA: one showed no benefits and the other showed marginal benefits only in the high-dose group. Even then, the clinical benefits amounted to delaying cognitive decline by about 3 months over the course of 1 year (Knopman & Perlmutter, 2021). The adverse effects related to aducanumab are also a cause for concern: headaches, falls, diarrhea, confusion, and amyloid-related imaging abnormalities (ARIA) (Salloway et al., 2022).

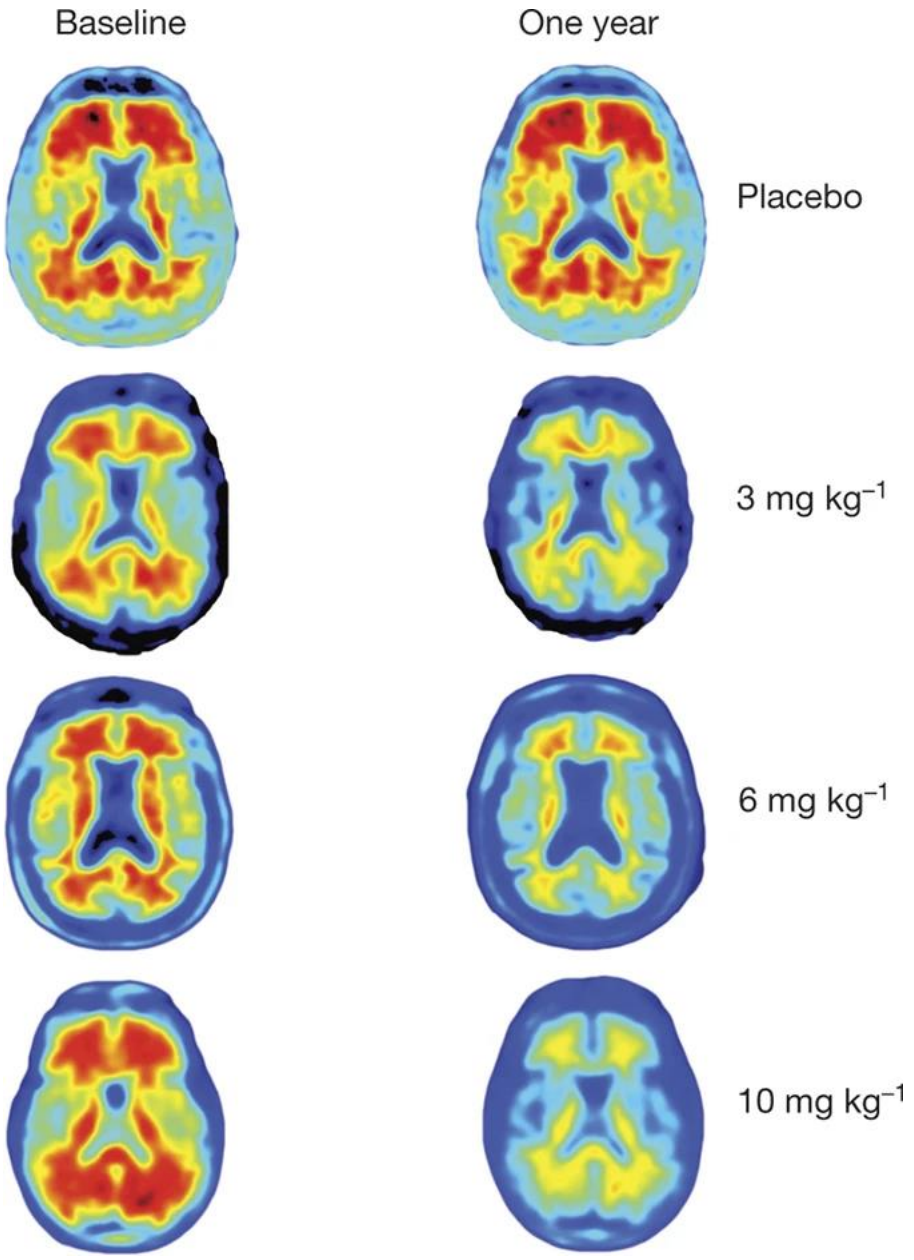

Figure 10: Aβ Plaque Reduction via Aducanumab
This figure shows where plaque reduction occurs in the brain while using aducanumab over the course of a full year. The comparison here is between placebo, low-dose, medium-dose, and high-dose courses. Taken from (Sevigny et al., 2016).

Donepezil

Donepezil was approved for human use in 1996 when the FDA granted approval to Pfizer Inc. and Eisai Company to sell donepezil in tablet form under the name Aricept. At that point, it became the second drug ever to be approved for AD treatment (“F.D.A. Approves Second Drug for Alzheimer’s,” 1996). Since tacrine is no longer used to treat AD, donepezil is the oldest of the six currently approved treatments. In 2022, Corium Inc. received FDA approval to sell donepezil for delivery through a transdermal system, or skin patch, under the name Adlarity (Stewart, 2022a). Donepezil is approved to treat all of the mild, moderate, and severe stages of AD (Kumar et al., 2022). As for the dosages of donepezil, Aricept can be taken as tablets of either 5 mg, 10 mg, or 23 mg once daily before bed, and Adlarity is to be used once weekly as a skin patch of either 5 mg or 10 mg (Winslow et al., 2011). Generic donepezil costs about $712 annually while Aricept costs about $6,599 (S. Sinha, 2022a). Similarly to Aricept, Adlarity comes in at an annual cost of about $6,284 (Stewart, 2022b). Donepezil is not disease-modifying but it can help alleviate some of the cognitive and behavioral symptoms (Kumar et al., 2022).

Functionally, donepezil is a cholinesterase inhibitor that functions in the brain and targets acetylcholinesterase, an enzyme that degrades acetylcholine after presynaptic release, with fairly high specificity. Its actions are rapid and reversible as it inhibits the ability of acetylcholinesterase to hydrolyze acetylcholine. That increases the amount of available acetylcholine at the

synapses within the brain thus enhancing cholinergic transmission of signals (Seltzer, 2005). Furthermore, donepezil may also have noncholinergic mechanisms: the upregulation of nicotinic receptors and the inhibition of voltage-gated sodium channels (Seltzer, 2007). Due to the fact that this drug is only used to alleviate symptoms, it is difficult to measure its efficacy. However, one paper, which conducted a meta-analysis on the results of 19 previously completed studies relating to the efficacy of donepezil, found that the results of 15 of those studies significantly favored treatment over placebo. Of the 4 that did not, 2 were due to the lack of a large enough pool of participants in the study (Di Santo et al., 2013). The majority of donepezil's side effects are mild and not long-lasting including insomnia, muscle cramps, fatigue, and anorexia, and gastrointestinal issues such as nausea, diarrhea, and vomiting are the most common (Bryson & Benfield, 1997). The more serious adverse effects are bradycardia, hyper- and hypotension, edema, weight loss, and nightmares. In rare cases, neuroleptic malignant syndrome and rhabdomyolysis have been reported (Seltzer, 2007).

Rivastigmine

In 1997, rivastigmine received approval for humans and became the second modern AD treatment to go into medical use (Patel & Gupta, 2022). This drug is marketed and sold by Novartis under the product name Exelon, and was also approved for transdermal delivery as the Exelon Patch in 2007 (*Novartis Receives Recommendation for Approval of Patch Formulation of Exelon, Only Skin Patch for the Treatment of Alzheimer's Disease in EU*, 2007). It is approved

for the treatment of mild to moderate AD as well as mild to moderate dementia from Parkinson's Disease (Khoury et al., 2018; Patel & Gupta, 2022). Exelon is available as twice-daily capsules of 1.5 mg, 3 mg, 4.5 mg, and 6 mg, while the skin patches come in 4.6 mg, 9.5 mg, and 13.3 mg daily (Patel & Gupta, 2022). At a unit price of $2.89, generic rivastigmine costs about $2,110 annually while generic rivastigmine patches cost about $1,799. However, Exelon Patch costs about $8,833 (Thornton, 2022). Unfortunately, no reliable pricing could be found for Exelon capsules.

Similar to donepezil, rivastigmine is also a cholinesterase inhibitor and it operates through the same mechanism of action. The difference between the two drugs is that rivastigmine also acts on butyrylcholinesterase, which is in glial cells and helps modulate cholinergic activity, in addition to acetylcholinesterase. The result is an overall increase in available acetylcholine in the brain (Kandiah et al., 2017). In 2013, a paper examining 7 other studies done on the efficacy of rivastigmine found treatment to be favored to placebo in all 7 studies, but it must be noted that the results were inconsistent between studies (Di Santo et al., 2013). However, a similar paper from 2016 concluded that rivastigmine was efficacious for the treatment of mild to moderate AD (Szeto & Lewis, 2016). The adverse effects are fairly similar to those of donepezil except for the fact that CNS symptoms are more commonly seen in donepezil and gastrointestinal symptoms are more common in rivastigmine (Hansen et al., 2008; Inglis, 2002).

Galantamine

Galantamine, the third and most recent of the cholinesterase inhibitors used to treat AD, was approved for human use in 2001, and is designed to treat mild to moderate AD (Lilienfeld, 2002; Thompson, 2001). Initially, the drug was branded as Reminyl and sold by Ortho-McNeil Neurologics, but it was renamed Razadyne in 2005 (“Reminyl Is Now Razadyne,” 2005). Unlike the previous two cholinesterase inhibitors that have been discussed, galantamine does not have a transdermal delivery method. Instead, Razadyne is offered as its normal instant release tablet or as Razadyne ER which follows an extended release design to make it easier for patients to adhere to their schedule (Seltzer, 2010). There is also no pharmacological difference between Razadyne and Razadyne ER nor is there a difference in their adverse effects. In fact, Razadyne had the largest patient persistence rate out of any of the cholinesterase inhibitors (Seltzer, 2010). Galantamine can be taken as either twice-daily immediate release tablets of 4 mg, 8 mg, or 12 mg, or as daily extended release tablets 8 mg, 18 mg, or 24 mg (Kalola & Nguyen, 2022). Razadyne ER costs about $4,219 annually, its generic version can be estimated to cost about $1,354, and generic galantamine immediate release costs about $1,949 (*Razadyne Uses, Side Effects & Warnings*, 2022). Unfortunately, there was no reliable pricing information regarding regular Razadyne.

Mechanistically, galantamine acts identically to its cholinesterase inhibitor counterparts, donepezil and rivastigmine, but it also displays a characteristic of

neither of the other two: it can be an allosteric potentiator for nicotinic acetylcholine receptors, thus facilitating the release of acetylcholine from presynaptic neurons and enhancing cholinergic transmission within the CNS (Kalola & Nguyen, 2022). As for efficacy, two separate analytical papers have deemed it efficacious for treatment of mild to moderate AD, but they also imply that questions remain (Di Santo et al., 2013; Szeto & Lewis, 2016).

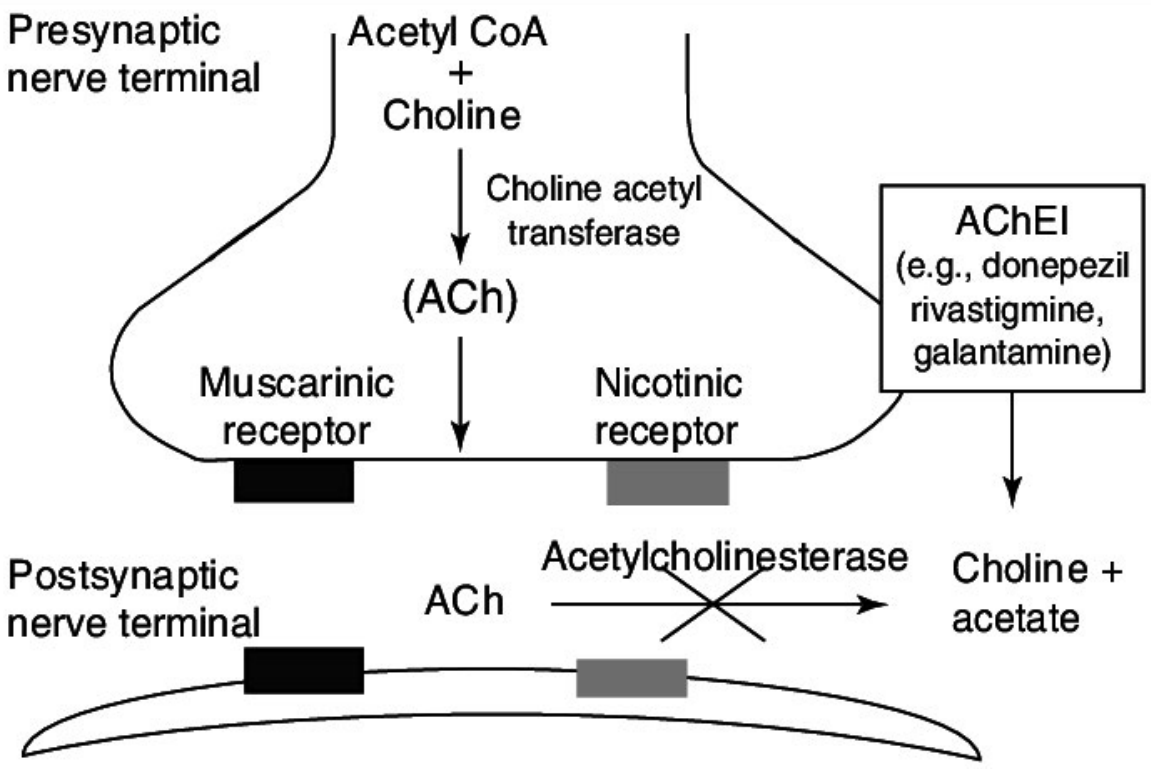

Figure 11: Cholinesterase Inhibitors Mechanism of Action
This is a simple diagram depicting the mechanism shared by the three cholinesterase inhibitors: donepezil, rivastigmine, and galantamine. Taken from (Moghul & Wilkinson, 2001).

Memantine

In 2003, memantine became the first non-cholinesterase targeting drug to become FDA approved for the treatment of AD as either an independent course of medication or in combination with one of the cholinesterase inhibitors (Thomas & Grossberg, 2009). Memantine, branded as Namenda, is manufactured by AbbVie, and, in 2013, Namenda XR was made available as an extended release medication leading to the discontinuation of the immediate release tablets in 2014. However, the immediate release Nameda can still be taken as an oral solution (Mondiello & Lam, 2015). This drug is approved for use in cases of moderate to severe AD, and it is currently the only AD treatment not indicated for use in cases of mild AD (Thomas & Grossberg, 2009). Namenda XR is taken daily in doses of either 7 mg, 14 mg, 21 mg, or 28 mg while regular Namenda can still be taken twice-daily as an oral solution in doses of 5 mg or 10 mg (Kuns et al., 2022). As for annual cost, Namenda comes in at about $5,840 and Namenda XR costs about $6,070, but there is no reliable pricing information regarding generic memantine options (S. Sinha, 2022b).

Unlike the three previous drugs that have been discussed, memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist that binds to the receptor uncompetitively and with moderate affinity (Thomas & Grossberg, 2009). The function of memantine is to affect a central mechanism in learning and memory: long-term potentiation (LTP). The way this happens is through the inhibition of calcium influx via NMDA receptors, which are found throughout the brain and

function in the mediation of LTP alongside their NT glutamate (Kuns et al., 2022; Thomas & Grossberg, 2009). Since glutamate, a principal excitatory NT in the CNS, is overstimulated in AD, the role of memantine is to counteract that overstimulation by uncompetitively binding to the NMDA receptor. That prevents glutamate from chronically activating the receptor, displacing magnesium, and allowing calcium to flow into the neuron and stimulate it. Memantine also has antagonistic ability towards serotonergic type 3 and nicotinic acetylcholine receptors (Rogawski & Wenk, 2003). In a paper that conducted a meta-analysis on the efficacy of memantine, it was found that half of the chosen studies did favor treatment with memantine while the other half was inconclusive (Di Santo et al., 2013). Although there remain conflicting ideas about the efficacy of memantine, there is no debate that it is considered to be safe for its population of users (Aarsland et al., 2009; Emre et al., 2010; Seppi et al., 2011). The only significantly common adverse effects are dizziness, headache, confusion, diarrhea, and constipation (Ditzler, 1991). The rare but more serious side effects include cerebral infarction, intracranial hemorrhage, seizure, myocardial infarction, peripheral edema, anemia, hepatitis, renal failure, respiratory infection, and neuroleptic malignant syndrome (Kuns et al., 2022).

Manufactured Memantine-Donepezil Combination

About 11 years after the FDA approved memantine for human use, it approved a manufactured combination of memantine and donepezil for the treatment of moderate to severe AD (Deardorff & Grossberg, 2016). The drug,

branded as Namzaric and manufactured by Actavis, is available as a capsule in doses of 10 mg of donepezil with either 14 mg or 28 mg of memantine (*Actavis Launches NAMZARIC™*, 2015; Deardorff & Grossberg, 2016). Annually, it costs about $6,979 to use this combination therapy (Durbin, 2022).

By combining the two drugs, their mechanisms have been put to work in conjunction, thus they simultaneously fight the effects of overstimulated glutamate while enhancing acetylcholine levels in the brain (Parsons et al., 2013). In 2012, an important study concluded that the efficacies of donepezil, memantine, and the combination were not different enough to warrant significance (Howard et al., 2012) . Between 2011 and 2015, various different analyses resulted in evidence that combining memantine with a cholinesterase inhibitor produced significant results as far as improved cognition (Atri et al., 2013; Gauthier & Molinuevo, 2013; Matsunaga et al., 2015; Tan et al., 2014). However, the clinical relevance of those results has been doubted (Farrimond et al., 2012). Nonetheless, in 2015, the European Federation of Neurological Scientists suggested that the use of combination therapy was more efficacious than simple treatment with a cholinesterase inhibitor (Schmidt et al., 2015). The adverse effects of the drug are essentially the same as those of each individual drugs, but they are safe to use both alone and together (Samy et al., 2010). The only additional side effect seen with significance is anorexia (Sheffrin et al., 2015).

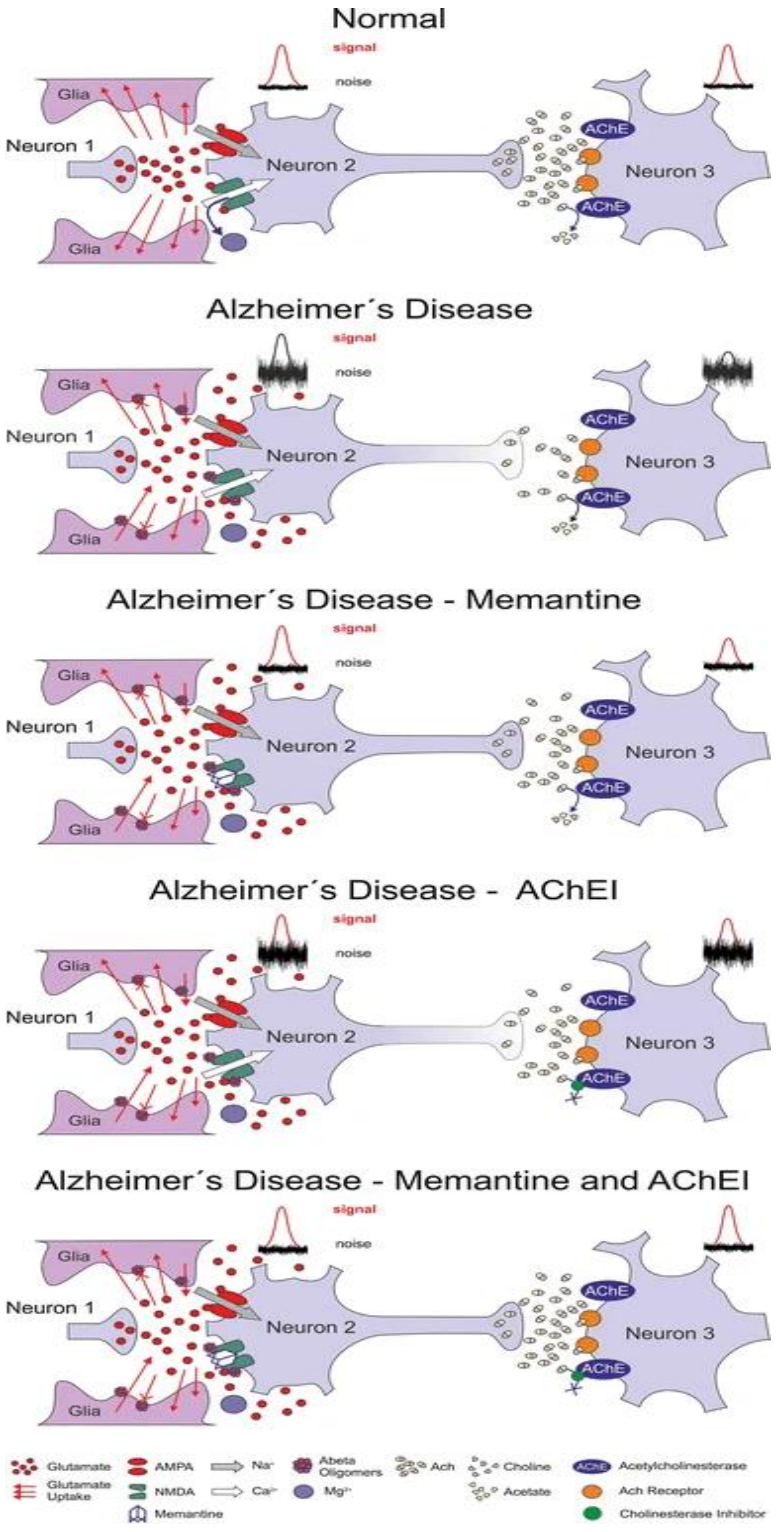

Figure 12: Complimentary Mechanisms of Memantine and Donepezil
Taken from (Parsons et al., 2013).

COST-BENEFIT ANALYSIS OF TREATMENT OPTIONS

Now that all of the topics essential to understanding AD, its pathogenesis, and how it can be treated have been covered, this paper can move into an analysis concerning the cost-effectiveness of the aforementioned treatment options. To effectively deliver that analysis, this paper will cite and discuss studies that have sought to quantify the cost-effectiveness of these drugs and their impact on quality of life. The following subsections will be individual evaluations of each drug, and the analyses made will later be used compare the drugs and make suggestions about the future of AD treatment options.

Aducanumab

Throughout its journey to approval, aducanumab was surrounded by controversy and was often the center of debates regarding whether or not it was worth using (Walsh et al., 2021). In order to investigate that dilemma, Sinha and Barocas developed a Markov state transition model of AD which would compare the cost-effectiveness of standard of care (SOC) versus using aducanumab over a theoretical 5-year period for 65-year-old people with mild AD. This simulates the progression of the disease from mild to severe, and it estimates the incremental cost-effectiveness ratio (ICER) which is $/QALY (P. Sinha & Barocas, 2022). The model, which accounts for all health care costs relating to AD over 5 years, estimated that costs with aducanumab are $255,440 and with SOC are $75,550. Meanwhile, the quality-adjusted life years (QALYs) with aducanumab were 2.93 QALYs and 2.46 QALYs with SOC. Compared to SOC

incrementally, aducanumab had an incremental cost of $179,890 and an incremental QALY of 0.47 thus an ICER of $383,080/QALY (P. Sinha & Barocas, 2022). Over a 30-year period, the model gave an ICER of $128,520/QALY, and, over 3 years, the ICER was $731,660/QALY. Lastly, assuming a willingness-to-pay (WTP) threshold of $100,000/QALY, the study found that aducanumab would not be cost-effective until the price was dropped down to $22,820 per year (P. Sinha & Barocas, 2022). Wittington et al conducted a similar study with similar results, but they used lower WTP thresholds and found that their cost-effective prices fell between $2,950 and $8,360 (Whittington et al., 2022).

Based solely on the presented data combined with the current cost, it seems that aducanumab is simply not cost-effective. When further considering the very questionable efficacy of the drug and the approval process marred in controversy, it is completely understandable if patients and their families avoid using this new treatment. Now, on the other hand, there certainly may be people out there whose WTP threshold, for one reason or another, exceeds $100,000/QALY. In those cases, they would probably give aducanumab at least a chance at improving their quality of life given that it is the only disease-modifying AD drug available and that its adverse effects are on par with the other AD drugs. However, all relative facts considered, it feels as though aducanumab at its current price tag is not the treatment that is going to help society take the next step forward in AD treatment and decrease both the patient-related and societal burdens of AD.

Donepezil

Given the lack of new treatments for AD, donepezil has remained amongst the most popular treatments since it became the first of the modern drugs to be approved, but its cost-effectiveness has been an ongoing discussion. In 2018, Chyr et al performed a study focused on determining the cost-effectiveness of donepezil in the treatment of AD. They used a Markov model set to produce theoretical estimates over 10 years of treating AD as it progresses through the stages of mild, moderate, and severe (Chyr et al., 2018). Their model found that no treatment costs $266,432 for 2.81 QALYs while treatment with donepezil costs $302,139 for 3.42 QALYs. Incrementally, that would mean that treatment with donepezil relative to no treatment would cost $35,707 for 0.61 QALYs with an ICER of $58,194/QALY. Assuming a WTP threshold of $100,000/QALY, they found that donepezil was cost-effective 89.37% of Monte Carlo simulations (Chyr et al., 2018). Additionally, a 2020 study from Thailand that included patients of all ages with all stages of AD found that, overall, the ICER associated with using generic donepezil versus SOC was $4,082/QALY. That study also found that the ICER decreased in direct proportion with decreased age of beginning treatment with donepezil (Kongpakwattana & Chaiyakunapruk, 2020).

Fortunately, the data presented here along with donepezil's longstanding history of effective use can lead to the conclusion that treatment with donepezil is, at the very least, worth trying. Despite arguments about its efficaciousness, it often proves to be a reliable drug as far combating the cognitive and behavioral

symptoms in all stages of AD, especially at its price level. Furthermore, it can be taken as either a daily tablet or as a weekly transdermal patch without a significant difference in price thus providing convenience to both patients and their caregivers. With an ICER of $58,194/QALY, donepezil falls well below the standard WTP threshold of $100,000/QALY and is likely to be within the budget of most people. Even if it does not, patients can resort to generic donepezil which is significantly more affordable at an ICER of $4082/QALY. Though concerns with a generic drug may exist, a 2015 study found no difference in quality of life when switching from Aricept to generic donepezil (Sakakibara et al., 2015).

Rivastigmine

Unlike aducanumab and donepezil, the less popular rivastigmine does not have as much concrete data relating to cost-effectiveness, so this section will present the best data that can be found. That sentiment is echoed by Loveman et al in their 2006 paper, which also states that their model resulted in an ICER of $67,471/QALY (Loveman et al., 2006). In 2013, a contrasting paper from Taiwan presented the results of a Markov cohort model meant to simulate AD progression from 65-years-old to death and progression from mild to moderate AD. Relative to no treatment, that model resulted in rivastigmine having 0.34 QALYs with a cost of $10,503 which leads to an ICER of $30,891/QALY (Chen & Lang, 2013). As for generic rivastigmine, a study from 2011 performed in the United Kingdom used both MMSE and MMSE-ADL models simulating a 5-year period to determine ICERs. The MMSE model, which is based solely on mental

state scores, resulted in an ICER of $12,522/QALY for the transdermal patch and an ICER of $17,938 for the capsules. The MMSE-ADL model, which includes daily living scores, resulted in ICERs of $10,788/QALY and $16,285 for the patches and the capsules, respectively (B. Nagy et al., 2011).

With the data available here, it is difficult to give a concrete opinion as to whether or not rivastigmine on its own would be worth the cost. Assuming that the WTP threshold of $100,000/QALY is still the standard, it is certainly reasonable to conclude that rivastigmine is worth a try and may even be very cost-effective depending on what data one considers. However, if one focuses on the data that suggest the highest ICER, it then becomes difficult to look at that number and believe that rivastigmine would be considered cost-effective by the majority of patients. Fortunately, the data regarding the generic version of this drug does appear to consistently show an ICER value that would be cost-effective for many patients and their families. Furthermore, rivastigmine becomes even more worthy when considering that the adverse effects are mostly gastrointestinal and that the ability to take the drug as a skin patch will then avoid all of those possibilities.

Galantamine

Similarly to rivastigmine, much of the literature surrounding galantamine is neither consistent nor entirely reliable due to vastly differing methodologies and the presence of industry-funded papers (Bond et al., 2012; Loveman et al., 2006). That being said, there are still sources where some information regarding

galantamine was found. For instance, in the same paper where Loveman et al posited the lack of reliability, those researchers also showed how their model came to an ICER result of $80,492/QALY even though another study that they evaluated had stated an ICER result of $10,290/QALY (Loveman et al., 2006). With the benefit of the doubt, it is possible that the difference could be due to generic versions versus the brand-name drug. However, when considering the fact that galantamine reduced the time spent in care by only 1.42-1.73 months over 5 years, it is more likely the result of a different methodology used for more favorable results (Loveman et al., 2006).

Assuming a WTP threshold of $100,000/QALY, the ICER of galantamine is certainly below that, but that does not mean that galantamine is worth its price tag. Relative to the other acetylcholinesterases, it has the highest ICER value by a significant amount. It also is extremely discouraging to see that it only reduces hospital time by 1.42-1.73 months over 5 years. It simply does not seem like an AD treatment worth trying, especially when considering that donepezil and rivastigmine are both more cost-effective and that aducanumab is at least disease-modifying to offset its price.

Memantine

Memantine, the only NMDA-antagonist, is relatively well researched due to its standing as a unique drug among AD treatments. One of the earliest studies covering memantine was the aforementioned Loveman et al paper published in 2006. In it, the researchers posited that the ICER value of

memantine was between $43,797/QALY and $61,552/QALY. They also stated treatment with memantine was found to increase financial savings and delay the progression of moderate to severe AD, and they believed that the cost-effectiveness of the drug may actually be underestimated (Loveman et al., 2006). In a 2013 paper, Hyde at al determined that, relative to SOC, memantine had 0.013 incremental QALYs and $479 in incremental costs for an ICER of $37,997/QALY. They also believe that memantine has shown improvements in functional efficacy and global impact as well as trending towards significant benefits in cognition and behavior. Furthermore, in probabilistic sensitivity analyses, they found that ICER values fell below $35,511 in 38% of simulations (Hyde et al., 2013).

Based on the ICER data presented, one might conclude that memantine is certainly cost-effective enough to be worthy of use. When considering how its cost-effectiveness improved between the publishing years of the studies discussed above, it is not farfetched to extrapolate such improvements and feel as though memantine is a drug that falls well within the means of many patients and their families. Nonetheless, there is also an argument against the drug when looking at the considerable adverse effects. Relative to the other AD treatments, there is a wider variety of rare yet potentially lethal conditions that can sometimes accompany memantine. The other pertinent drawback is that it is not approved for use in cases of mild AD, which may mean that quality of life is already significantly diminished by the time memantine may provide beneficial treatment.

Manufactured Memantine-Donepezil Combination

Unfortunately, due to lack of access, there was not a significant amount of research to be found regarding the cost-effectiveness of the memantine-donepezil combination treatment. However, Knapp et al published a study in 2017 that delivers the results of cost-effectiveness models on donepezil plus memantine relative to using only donepezil in moderate to severe AD (Knapp et al., 2017). Their analyses, from both a societal perspective and from a health and social care perspective, showed that the combination drug had a slightly higher but not statistically significant difference in cost while not showing any clinical benefits of significance. The results showed that the combination would be more cost-effective than donepezil alone in only 50-60% of cases. Relative to donepezil, the memantine-donepezil combination had an ICER of $23,552/QALY (Knapp et al., 2017).

While there cannot be an evaluation made on the cost-effectiveness of the memantine-donepezil combination relative to SOC because of lack of access to research or in mild AD because it is not approved for such use, there is something to be said about this drug in moderate to severe AD. Considering that the ICER value falls well within most WTP, it seems that the combination treatment is worthwhile in cases of moderate to severe AD. The only concern regarding this situation is that the study results implied that the clinical benefits were not statistically significant, although there were slight benefits.

Table 4: Summary of ICER Values

Treatment Option	ICER Value
Aducanumab	$383,080/QALY
Donepezil	$58,194/QALY
Generic Donepezil	$4,082/QALY
Rivastigmine	$30,891/QALY
Galantamine	$80,492/QALY
Memantine	$37,997/QALY
Memantine-Donepezil Combination	$23,552/QALY (relative to donepezil)

*This table provides a simple summary of the most relevant ICER values that can be found throughout this section of the paper. Note that the ICER value corresponding to the Memantine-Donepezil Combination is relative to donepezil while the rest of the values are relative to SOC.

CONCLUSIONS AND SUGGESTIONS

Based on the ICER values presented in Table 4 and assuming a WTP threshold of $100,000/QALY, there is only one AD treatment option that is immediately ruled out: aducanumab. This drug is prohibitively expensive, and, although it is the only disease-modifying treatment available, it is surrounded by controversy and lacks data that can show a significant efficaciousness or a worthwhile cost-effectiveness the fight against AD.

Now, if the WTP threshold is decreased to the low side of the generally accepted range at $50,000/QALY, only three drugs remain: generic donepezil, rivastigmine, and memantine. So, as far as affordability goes, rivastigmine is the most cost-effectiveness brand-name acetylcholinesterase while donepezil has the most cost-effective generic version. Memantine also appears to be a relatively affordable and beneficial option if a patient or their family determines that its targeted symptoms are more appropriate than the acetylcholinesterases. Some people may feel safer using brand-name drugs, but this thesis suggests that generic donepezil and memantine are the two most cost-effective drugs in the treatment of AD. The most relevant differences between the two are that generic memantine is not readily available, what symptoms they combat, and their annual pricing, but both are worthwhile.

However, if one of the two had to be chosen as the best treatment options, that would be generic donepezil for a few reasons: it has the most cost-effective ICER by a wide margin, it can be administered in whatever form is most

convenient between oral tablets or skin patches, and it is approved to treat all three stages of AD so patients do not have to change their routines as their disease state progresses. Regardless of which treatment is used, it is more cost-effective to continue the use of either of the drugs than it is to discontinue such use (Knapp et al., 2017). The question now becomes: why not opt for the memantine-donepezil combination treatment? The answer is simply that the combination drug is not more cost-effective than continuing treatment with only donepezil or only memantine (Knapp et al., 2017).

Going forward, this thesis suggests that the treatment of the disease should be started as early as possible regardless of what drug is used. There are several instances in this paper where the data suggests that earlier and longer treatments are most cost-effective. For example, a Markov model on aducanumab concluded that 30 years of treatment was significantly more cost-effective than 3 years (P. Sinha & Barocas, 2022). Also, the cost-benefit analysis sections on rivastigmine and memantine discussed how the cost-effectiveness of the drugs had improved over the years. Furthermore, Green at al published a study in 2019 that showed that actively treating dementia patients prolonged the time they spent in the mild CI stage and reduced the time the patients spent in all three of the AD stages, as seen below in Figure 13 (Green et al., 2019).

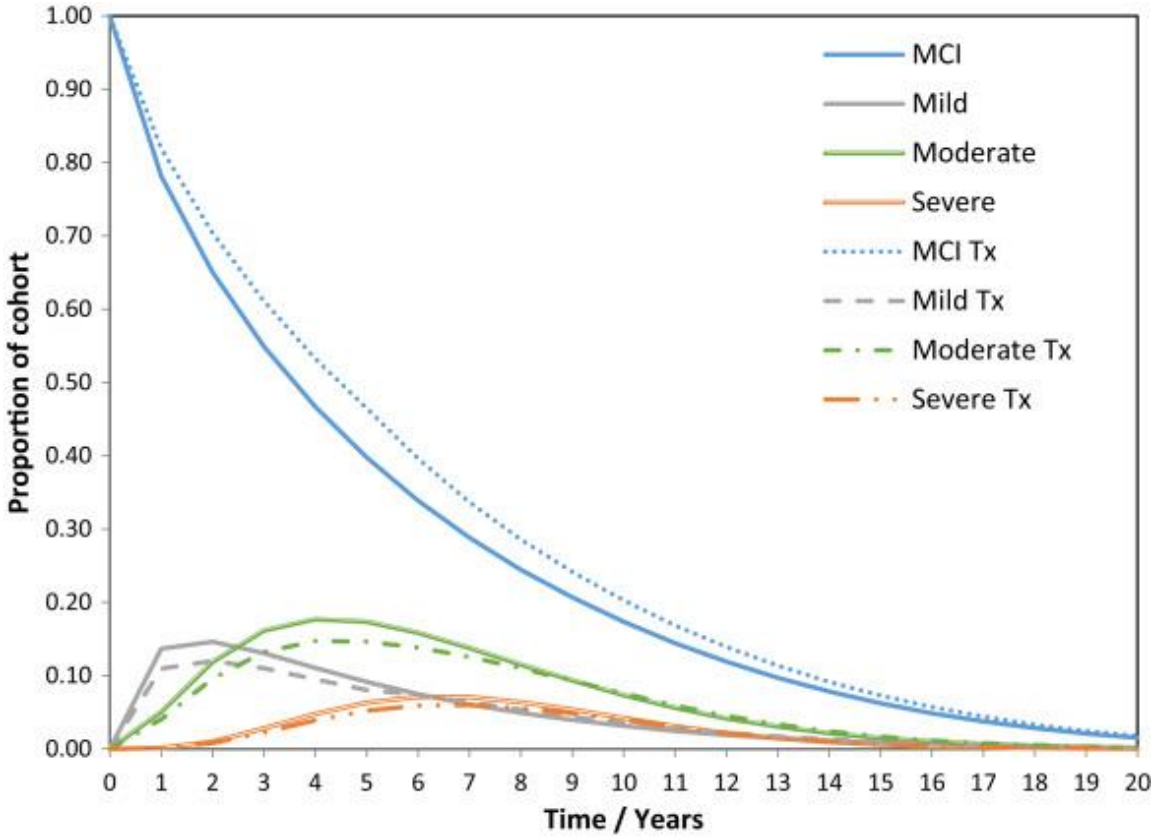

Figure 13: Time Spent in Disease State by Proportion of Cohort
This figure depicts the results from Green et al in 2019 where their results show that early treatment (indicated by Tx) of potential AD patients can prolong the time spent in mild cognitive impairment (MCI) and reduce time spent in mild, moderate, and severe AD. Taken from (Green et al., 2019).

In addition to the previous suggestion, this thesis also finds that the study of aducanumab should become the priority of AD researchers. Without industry influence, further research can provide doctors, patients, and caregivers with the answers necessary to determining whether aducanumab is worth it. This can also hopefully lead to a decrease in the price of aducanumab to a level where it is actually cost-effective for society. Furthermore, such research is currently the best chance that society has for finding a drug that can halt the progression of

AD. There has never before been a treatment option that can actively decrease both the amount of Aβ plaques and the levels of tau phosphorylation in the brain. While aducanumab may not be the solution to the societal problem that is AD, it is a significant step in the right direction.

Lastly, the ongoing public health dialogue regarding AD and other forms of dementia must continue to be a priority and must be spread further. These diseases have become an immensely impactful burden on society and especially on those directly affected by them. It is essential that the general population understand the impact of AD so that awareness can continue to be raised. This will enable public health discussions that can lead to policies limiting the financial toll on patients and inevitably making treatments more cost-effective.

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