Alzheimer's: Advancements through research

Taylor Wrozek
Western Michigan University, taylormwrozek@gmail.com

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Alzheimer’s

Advancements through research

Taylor Wrozek
4/8/2017
Abstract

This literary review examines some genes and proteins such as presenilin 1, presenilin 2, amyloid precursor protein, and apolipoprotein E, and Tau that are associated with Alzheimer's disease. It also delves into four causal hypotheses for Alzheimer's disease: the oxidative stress-induced AD cascade hypothesis, the copper-2 hypothesis, the amyloid cascade hypothesis, and the type II diabetes mellitus hypothesis. It further explains some of the current ways of diagnosing Alzheimer's disease and its different forms; symptoms that have been associated with Alzheimer's disease; and the different demographics of Alzheimer's disease. Finally, different treatments, preventions, risks, and current research for Alzheimer's disease is reviewed.

Overall, Alzheimer’s has been shown to affect non-Hispanic white populations between the ages of 75-85 years old the most (Herbert et al. 2003, Plassman et al. 2007, Herbert et al 2013). Significant contributors to the disease included type II diabetes, cardiovascular diseases, and diets high in saturated and trans-unsaturated fats (Luchsinger et al. 2001, Morris et al. 2003, & Elias et al. 2004). A number of studies have found that a healthy diet that includes a moderate amount of fish, continued physical exercise, and continued mental exercise may help decrease the effects of Alzheimer’s disease and dementia (Wang et al. 2006, Feart et al. 2010, &Kivipelto & Håkansson 2017).
Introduction

Alzheimer’s disease (AD) is the most common form of dementia making up two-thirds of all dementia cases (Guttmacher & Collins 2003). There has been a substantial amount of advancement since the initial description of Alzheimer’s disease in 1906 (Tagarelli et al. 2006). However, it remains difficult to pin-point exact causes; and new criteria for diagnosis of AD are continually being formed (Serrano-Pozo et al. 2014). There is also still an extensive debate regarding relationships between autopsy neuropathological findings and AD correlation (Nelson et al. 2013).

Throughout this literary review I will examine genes and proteins associated with AD, current causal hypotheses for AD, biochemical changes with AD, symptoms of AD, and the most current method of diagnosing AD. Continuing forward I will look at the demographics of AD, possible ways to reduce the risk of developing AD, and current treatments of AD. Finally, I will delve into some of the current studies taking place today involving AD diagnosis, treatment, and prevention.

Genes & proteins associated with AD

There are four readily confirmed genes associated with Alzheimer’s disease: presenilin 1 (PSEN1), presenilin 2 (PSEN2), amyloid precursor protein (APP), and apolipoprotein E (APOE) (Williamson et al. 2009). The Tau protein is also highly associated with AD (Kimura 2016). PSEN1 gene provides instructions for the presenilin 1 protein which is a proteolytic subunit of gamma-secretase. PSEN2 gene similarly provides instructions for the presenilin 2 protein which is another subunit of gamma-secretase and has also been linked to mitochondria-dependent apoptosis. The gamma-
secretase enzyme cleaves transmembrane proteins into peptides and is involved with the cutting of APP into soluble amyloid precursor protein (sAPP) and several versions of amyloid-beta (Aβ) peptide. sAPP shows growth promoting properties and is perhaps involved in the differentiation, development, or synaptic function of nerve cells (Thinakaran & Parent 2004). APP is a single-pass transmembrane protein; its function is not definitive although it has been shown to have a positive effect on cell health and growth when overexpressed. APP has also been shown to modulate cell growth, motility, neurite growth, and cell survival in transiently infected lines (O’Brien & Wong 2011). APOE combines with lipids to form lipoproteins which provide movement of cholesterol through the vascular system. It has three main alleles: e2, e3, and e4, with e3 being the most common (Ashford 2004). Tau proteins are associated with the stabilization and flexibility of microtubules in neurons. They are derived from the alternative splicing of microtubule-associated protein tau gene (Mandelkow et al. 1995). It is essential to understand PSEN1, PSEN2, APP, APOE, Tau, and all of their relations to move forward. I will discuss them and their functions within AD further throughout the remainder of the paper.

Causal hypotheses

There are many hypotheses that attempt to explain the cause of AD in order to try to find a possible treatment, prevention, and/or cure for the disease. Following I will discuss four varying hypotheses: the oxidative stress-induced AD cascade hypothesis, the copper-2 hypothesis, the amyloid cascade hypothesis, and the type II diabetes mellitus hypothesis.
The oxidative stress-induced AD cascade hypothesis states that AD patients and animal models show oxidative damage to their neurons prior to amyloid plaques and neurofibrillary tangles. Oxidative stress occurs when some of the free radicals used during aerobic respiration within mitochondria escape and cause alterations on other macromolecules within a cell (Bonda et al. 2014). These alterations may cause proteins to become insoluble or aggregate abnormally by promoting protein cross-linkages and impaired proteolysis (Zhu et al. 2012 & Domenico et al. 2013). Oxidation of deoxyribonucleic acid/ribonucleic acid may also lead to fragmentation and defects in essential repair machinery (Nunomura et al. 2012 & Bradley-Whitman et al. 2014.) It is also noted that oxidative stress appears to be selective in AD patients—being found in areas such as the hippocampus and cortex, but not the cerebellum (Sultana & Butterfield 2013). This selectivity is predicted to be a result of the higher metabolic demands seen in neurons with long axons and multiple synapses. This hypothesis does suffer some shortcomings, however, as it is unable to explain the predictable and consistent spread of neurodegeneration throughout distinct regions within the brain (Bonda et al. 2014).

The copper-2 hypothesis proposes that AD is caused from the consumption of inorganic copper from drinking water traveling through copper piping and copper containing supplement pills (Brewer 2017). Some evidence in support of this hypothesis includes the accelerated cognitive decline in those with a high intake of copper and a high diet of both saturated and trans fats (Morris et al. 2006) and AD being more prominent after the 20th century in developed countries compared to both underdeveloped countries and the years prior to the 20th century. The hypothesis
furthers that this increase in AD cases is not due to increased life-spans seen after the 20th century, but because of increased development in living styles. The support for this argument shows that there is an increased percentage of cases in those diagnosed with AD in developed countries compared to underdeveloped countries. They further argue that if AD cases increased due to increased life-span, then AD cases would have been seen more often or described more often prior to the 20th century in cases where there were large populations of citizens over the age of 60 years old in France and the US prior to the 20th century (Brewer 2017).

The amyloid cascade hypothesis predicts that the primary influence of AD pathology is caused by the accumulation of Aβ in the brain. The other hallmarks of AD are proposed to be a result from an imbalance in Aβ production and clearance (Hardy & Selkoe 2002). The hypothesis contends that Aβ accumulation leads directly to a cascade of synapse loss, plaque deposition, inflammation, hyperphosphorylation, and finally death of neurons. According to the hypothesis, familial AD is caused by a mutation in either APP, PSEN1, or PSEN2 genes that cause an accumulation of an amyloid peptide that has a high tendency to form β-pleated sheets which aggregate into oligomers and plaques. It furthers that sporadic AD develops when an individual’s personal history expedites normal age-dependent Aβ accumulation. In either case, Aβ accumulation triggers an immune response which in turn stimulates more Aβ production (Herrup 2011).

The type II diabetes mellitus hypothesis predicts that AD pathology is aggravated and perhaps even induced by aberrant insulin signaling. This hypothesis is grounded on the fact that neurofibrillary tangles are caused from the accumulation of aggregated...
Tau; Tau aggregations are produced from the hyperphosphorylation of Tau; and that the hyperphosphorylation of Tau can be caused by the abnormal activation of glycogen synthase kinase 3β which can be induced by insulin deficiency/resistance seen in those with diabetes mellitus (Kimura 2016). Type II diabetes mellitus may also induce Aβ accumulation through a change in the pathway of the intracellular transportation via endocytosis of APP and beta site amyloid precursor protein cleaving enzyme 1 (Koh et al. 2005 & Okabayashi et al. 2015). Evidence of Aβ pathology induced by type II diabetes has been shown in nonhuman primate brains (Okabayashi et al. 2015). Some recent studies have also shown improvement in the cognition of those with AD with use of intranasal insulin (Craft et al. 2012 & Claxton et al. 2015).

**Diagnosis, biochemical changes, & symptoms**

Mild cognitive impairment (MCI) is an initial diagnosis that can lead to the development of AD. MCI can be seen as a change in cognition from baseline. In order to be diagnosed with MCI, one most show decline in one or more cognitive domains, including, yet not limited to: memory, executive function, attention, language, and visuospatial skills—with episodic memory being most common in those that develop AD. Patients must be able to perform functional tasks independently although they may be less efficient, slower, or make more errors performing these functional tasks in order to receive diagnosis of MCI. The patient’s cognitive changes should also be mild enough that there is no significant impairment during social or occupational functioning. Finally, vascular, traumatic, and medical issues that could account for cognitive decline should be ruled out. Otherwise, the patient has the potential for being diagnosed with dementia. In order for MCI to be strongly diagnosed as MCI due to AD, there should be
an autosomal dominant mutation in APP, PSEN1, or PSEN2; or the patient should be APOE e4 positive (Albert et al. 2011).

AD disease, itself, can be diagnosed with evidence of Aβ peptide plaque build-up, tau neurofibrillary tangles, or neural injury (Albert et al. 2011). Evidence of Aβ peptide plaque build-up can be confirmed with measurements of low amyloid-beta42 levels in the cerebrospinal fluid (Blennow & Hampel 2003, Selkoe 2005, Shaw et al. 2009) and positive Pittsburgh Compound-B binding measurements via positron-emission tomography (PET) (Fagan et al. 2006). Elevated cerebrospinal fluid measurements of tau or phosphorylated-tau provide evidence of both tau neurofibrillary tangles and neural injury (Blennow & Hampel 2003, Selkoe 2005, Shaw et al. 2009). Other measurements of neural injury include brain atrophy and hypometabolism or hypoperfusion measured using magnetic resonance imaging (MRI), PET, and single-photon emission computed tomography imaging (Atiya et al. 2003, Jagust 2006). Other biochemical changes that can be accompanied with AD include cell death, synaptic damage, oxidative stress, or inflammation. Patient’s with positive amyloid-beta biomarker and a positive biomarker of neuronal injury have a high likelihood of being diagnosed with/developing AD. Patient’s with only one or the other have an intermediate likelihood of being diagnosed with/developing AD (Albert et al. 2011).

Generally, there are two accepted forms of AD. The first is early onset Alzheimer’s disease which occurs before the age of 60-65; and the second being late onset Alzheimer’s disease which occurs after age 60-65 and is considered the predominant form of AD (Bertram & Tanzi 2005). Aside from these two forms, there are three more categories of AD diagnosis, including autosomal dominant, familial, and
sporadic cases. To be diagnosed with autosomal dominant AD, there must be at least three individuals in two or more generations of a family diagnosed with AD with two of the three being first-degree relatives of the third. Autosomal dominant AD represents <5% of AD cases. Familial AD involves more than one individual being diagnosed with AD and those diagnosed being third degree relatives or closer. This type of AD represents 15-25% of all cases. Finally, sporadic AD involves an isolated case in a family or cases with more than three degrees of relationship between them. This (Goldman et al. 2011).

General symptoms given by the Alzheimer’s Association of AD include memory loss that disrupts daily functional task, difficulties with planning or problem solving, difficulty completing familiar functional task, confusion of time or location, vision problems, problems with speech and comprehension, losing items, decreased decision making skills, withdrawal from social activities, and changes in mood and personality (alz.org 2017). However, findings show that the olfactory, visual, auditory, and motor systems are all affected by AD pathology (Table 1). Some of these symptoms include impaired odor identification, concomitant eye diseases, speech perception impairments, hearing loss, and various motor impairments. On their own these effects can seem coincidental to aging; however, these effects along with positive APP, PSEN1, PSEN2, or APOE findings may help diagnose the potential for Alzheimer’s prior to any cognitive impairment (Albers et al. 2015).
**Demographics of Alzheimer's**

Overall, the numbers of people affected by AD are shown to be growing. In 2000, 4.5 million were reported to have AD in the US with 7% between the ages of 65-74 years old (y.o.), 53% between 75-84 y.o., and 40% being over 85 y.o (Herbert et al. 2003). In 2010, 4.7 million were reported to have AD in the US with 14% between the ages of 65-74 y.o., 49% between 75-84 y.o., and 37% being over 85 y.o (Herbert et al. 2013) (Figure 1). It was estimated in 2012, that there were 24 million people worldwide with AD and it was predicted that this number will double every 20 years (Mayeux & Stern 2012).

When reviewing AD occurrence and differences in both men and women, some studies have noted AD occurrence to be significantly higher in women compared to men. It was also noted that these differences may be because women on average live longer than men (Plassman et al. 2007, Mielke et al. 2014, Podcasy & Epperson 2016). Women have also been shown to be diagnosed earlier and their symptoms to progress faster; but men with AD are shown to live shorter lives than women with AD (Todd et al 2013, Podcasy & Epperson 2016) Risk factors that contribute to AD such as smoking, coronary artery disease, and brain injury with loss of consciousness are more common among men. Diabetes, obesity, and hypertension are also more common among men, but pose a higher risk when in women for AD. Greater life-long exposure to estrogen may also increase risk of AD contributing to women's diagnosis of AD (Podcasy & Epperson 2016).
Very few studies included demographics on race/ethnicity as most studies were largely of those who consider themselves to be Caucasian. One study, however, shows AD population to be made up of 82.1% non-Hispanic white people, 12.9% non-Hispanic black people, and 5% to be Hispanic people (Plassman et al. 2007).

**Risk reduction & risk contribution**

There are many possible associations between risk reduction, risk contribution, diseases, and life habits (Table 2). For example, populations with prototypical AD manifestations have been shown to present with cerebrovascular disease more often than not suggesting that the presence of a cerebrovascular disease may contribute to AD (Schneider & Bennett 2010). Mid-life hypertension has also been considered a contributor to late onset dementia (Yamada et al. 2003, Elias et al. 2004, Whitmer et al 2005). Risk of AD has been shown to approximately double with presence of type II diabetes (Luchsinger et al. 2001, Farris et al. 2003, Luchsinger et al. 2004). It has also been suggested that Diabetes directly affects Aβ accumulation in the brain due to hyperinsulinemia competing for the insulin-degrading enzyme thereby disrupting Aβ clearance (Farris et al 2003). Several studies have been able to link high and low weights, weight gain, and weight loss to increasing the risk of AD (Gustafson et al. 2003, Brubacher et al. 2004, Buchman et al. 2005, Stewart et al. 2005, Atti et al. 2008). After traumatic brain injury, Aβ deposition (Iwata et al. 2002) and intraneuronal tau pathology—which both are associated with AD—are increased (Smith et al. 2003). Poor life habits such as high consumption of saturated fats (when compared to low consumption of saturated fats) can double the incident risk of AD; while trans-unsaturated fats consumption triples incident risk of AD (Morris et al. 2003).
On the other hand, a lower risk of dementia is seen in those with higher education (Roe et al. 2008). Good life habits such as the consumption of N-6 polyunsaturated fats and monounsaturated fats (Morris et al. 2003) and weekly consumption of fish along with regular consumption of omega-3 rich oils have also been shown to reduce incident risk of AD (Barberger-Gateau et al. 2007). Mediterranean diets have been associated with slower cognitive decline and reduced risks of AD (Scarmeas et al. 2006, Feart et al. 2010). Furthermore, increased physical exercise has been shown to serve a beneficial role in the reduction of AD risk (Podewils et al. 2005, Larson et al. 2006, Wang et al. 2006).

**Treatment & prevention strategies**

There are few treatment options when it comes to AD (Table 3). There are a few of the common AD symptoms along with the current treatment strategies for them, such as the following:

1) The nucleus basalis of Meynert is a large source of cholinergic innervation of the cerebral cortex and also an area that shows greater than 70 percent degeneration in patients with AD (Whitehouse 2006). Successful therapy has been shown to slow the progression of AD with acetylcholinesterase inhibitors such as donepezil, galantamine, and rivastigmine that prevent 2 months per year of decline in AD patients (Trinh et al. 2003).

2) In the brains of AD patients, glutamine synthetase is oxidized leading to excess glutamate which excessively activates N-methyl-D-aspartate (NMDA) receptors
causing neuronal degeneration. Significant reduction in cognitive decline in moderate-to-severe AD has been shown with the use of memantine (Reisberg et al. 2003).

3) A variety of antidepressant medications can be used to treat symptoms of AD such as agitation. Some of these medications include citalopram, fluoxetine, paroxetine, and sertraline. (Cipriani et al. 2012, Peters et al. 2016) Two benzodiazepines (lorazepam and oxazepam) are generally used in the treatment of verbal disruptive behavior and resistance in AD patients (Defrancesco et al. 2015). Finally, severe agitation, aggression, and psychosis can be treated with antipsychotics such as aripiprazole, clozapine, haloperidol, olanzapine, and quetiapine although this can lead to increased risk of cerebrovascular events and death (Herrmann & Gauthier 2008).

One prevention strategy is the consumption of Mediterranean diet which consists of a high intake of vegetables, legumes, fruits, and cereals; high intake of unsaturated fatty acids and low intake of saturated fatty acids; moderately high intake of fish; low intake of dairy products; low intake of meat; and a moderate amount of wine. This diet has been shown to lower mortality in AD and overall risk of AD (Scarmeas et al. 2006).

A more recent clinical trial known as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) has also proposed a prevention strategy based on evidence from their clinical trial involving nutritional guidance, physical exercise, and cognitive training. The diet promoted fruits, vegetables, whole grains, rapeseed oil, and a fish meal twice a week; meanwhile, it restricted trans-fat, refined sugars, and alcohol. The physical exercises were gradually increased from 30 minutes of muscle-strength training, aerobic exercise, and postural balance twice a
week to 60 minutes two to three times a week. Finally, the cognitive training included
tasks to improve executive function, memory improvement, and mental speed. Overall,
the clinical trials showed significant evidence that a good diet and physical/mental
exercise can help to improve a person cognitive function (Kivipelto & Håkansson 2017).

**Current Research**

AD research is a continuous process. Some of the new trials that are currently
being conducted involve: the treatment of cognitively normal individuals with genetic-
based risk of developing AD (API-ADAD and API_APOE4 Treatment Trial); the
monitoring of subjects and families with Autosomal-Dominant AD (DIAN-TU); testing of
solanezumab effectiveness on the prevention of sporadic AD in cognitively normal
adults with high levels of amyloid in the brain (A4 Trial); and the use of pioglitazone
(normally used for diabetes mellitus) on cognitively normal adults who are positive for
the translocase of outer mitochondrial membrane 40 homolog gene (TOMM40) and

One recent study involving therapeutic strategies using synthetic peptides or
monoclonal antibodies to decrease Aβ build up in the brain is still ongoing with high
expectations for clinical trials, but safety and difficult adverse effects during active
immunotherapy using the synthetic peptide cause need for concern and obvious
drawbacks. Passive immunotherapy uses monoclonal antibodies with fewer problems
arising in comparison (Barrera-Ocampo & Lopera 2016).

Another recent study investigates the uses of repeated MRI-guided ultrasound
treatments for a noninvasive, temporary, and localized opening of the blood brain
barrier (BBB) to improve drug delivery. This method shows an improvement in the spatial memory of AD transgenic mice and could potentially lead to a decrease in plaque build-up and increased neural plasticity (Burgess et al. 2014).

A broad study involving the Alzheimer’s Disease Neuroimaging Initiative (ADNI) is working toward characterizing clinical, genetic, imaging, and biochemical biomarkers of AD. They also are working on the development of optimized and standard methods for AD research that can be used to make large shared databases that could increase research advancements. Their hope is to identify a combination of biomarkers that will lead to a more accurate and early diagnosis of AD (Weiner et al. 2013).

Discussion

Alzheimer’s disease remains a continuous topic of research although it is probable that the subject may shift from prevention of the disease to early detection and treatment similarly to cancer research (Hsu & Marshall 2017). Most causes of the disease remain unknown as it is unclear whether many of the hallmark features are the cause of the disease or caused by it. Further investigation is therefore needed into the etiology of the disease.

Prevention research could be furthered with potential studies on daily mental exercises in the prevention of Alzheimer’s Disease. Mental exercises could include continued reading, brain games, or recreational educational classes among others. Forms of treatment research could be developed looking at the aspects of an Alzheimer’s patient’s living situation with the question involving the difference in
cognitive decline in those living with family, those with assisted living, and those living in geriatric homes.

With the numbers of those with Alzheimer's continuously rising and the average person living on to an older age it is pertinent to continue on with Alzheimer's disease and other dementia research (Raftery et al. 2014).
# Tables and Figures

<table>
<thead>
<tr>
<th>System</th>
<th>Pathology presence</th>
<th>Pathology symptoms</th>
<th>Cognitively Normal Adults Presence</th>
<th>AD Patients Presence</th>
<th>Transgenic mice overexpressing Aβ, tau, or APP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfactory System</td>
<td>Peripheral and central olfactory neural network</td>
<td>Impaired odor identification</td>
<td>Some show impaired odor identification associated with AD pathology presence</td>
<td>Most show impaired odor identification associated with AD pathology presence</td>
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</tr>
<tr>
<td>Visual System</td>
<td>Peripheral and central pathways of the visual neural system; visual association cortical areas</td>
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<td>Most show AD pathology in peripheral and central pathways of the visual neural system</td>
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<td>Auditory System</td>
<td>Central area of the auditory neural pathway</td>
<td>Impairments in speech perception and hearing loss</td>
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<td>AD pathology in primary auditory cortex associated with changes in auditory evoked responses</td>
</tr>
<tr>
<td>Motor System</td>
<td>Motor neurons of the pyramidal motor pathways and extrapyramidal motor pathways</td>
<td>Various motor impairments</td>
<td>Motor impairment is highly prevalent in older adults; hypoxexcitability in the primary motor cortex</td>
<td>Hyperexcitability in the primary motor cortex, a substantial amount experience pyramidal and extrapyramidal motor impairments</td>
<td>AD pathology is associated with significant motor neuron impairments at the cellular and behavioral levels</td>
</tr>
</tbody>
</table>

*Table 1 consolidates the effects of AD pathology on the different sensory and motor systems and the overall prevalence in cognitively normal adults, AD patients, and transgenic mice. All findings are from a 2015 author manuscript by Albers et al.*
<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on incident of AD</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher Education</td>
<td>Reduces risk</td>
<td>(Roe et al. 2008)</td>
</tr>
<tr>
<td>Type II Diabetes</td>
<td>Doubles risk</td>
<td>(Luchsinger et al. 2001, Farris et al. 2003, Luchsinger et al. 2004)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Contributes to risk</td>
<td>(Schneider &amp; Bennett 2010)</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>Contributes to risk</td>
<td>(Smith et al. 2003)</td>
</tr>
<tr>
<td>High consumption of saturated fats</td>
<td>Doubles risk</td>
<td>(Morris et al. 2003)</td>
</tr>
<tr>
<td>Trans-unsaturated fats consumption</td>
<td>Triples risk</td>
<td>(Morris et al. 2003)</td>
</tr>
<tr>
<td>N-6 polyunsaturated fats and monounsaturated fats</td>
<td>Reduces risk</td>
<td>(Morris et al. 2003)</td>
</tr>
<tr>
<td>Fish and/or omega-3 consumption</td>
<td>Reduces risk</td>
<td>(Barberger-Gateau et al. 2007)</td>
</tr>
<tr>
<td>Mediterranean diet</td>
<td>Reduction in risk</td>
<td>(Feart et al. 2010)</td>
</tr>
</tbody>
</table>

*Table 2 examines different factors that involve diseases, injuries, or life choices and how they affect the risk of developing AD.*
Table 3.  
AD Medications, their functions, success, and side effects

<table>
<thead>
<tr>
<th>Area of interest(AOI)</th>
<th>Function of AOI</th>
<th>Function of Medicine/Medication s</th>
<th>Success of Medication</th>
<th>Side effects</th>
<th>Source</th>
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<tr>
<td>Nucleus basalis of Meynert</td>
<td>Cholinergic innervation of the cerebral cortex</td>
<td>Acetylcholinesterase inhibitors: donepezil, galantamine, and rivastigmine</td>
<td>Prevention of 2 months per year of decline in AD patients</td>
<td>Facial flushing, dyspepsia, nausea, vomiting, and diarrhea</td>
<td>(Trinh et al. 2003)</td>
</tr>
<tr>
<td>Glutamate in Cortical and hippocampal neurons</td>
<td>Principle excitatory neurotransmitter</td>
<td>Glutamate gated NMDA channel blocker: memantine</td>
<td>Significant reduction of cognitive decline in AD patients</td>
<td>Dizziness, and low frequencies of confusion and hallucinations</td>
<td>(Reisberg et al. 2003)</td>
</tr>
<tr>
<td>Serotonin reuptake</td>
<td>Can cause agitation</td>
<td>Selective serotonin reuptake inhibitor: citalopram, fluoxetine, paroxetine, and sertraline</td>
<td>Can decrease agitation in AD patients</td>
<td>Drowsiness, nausea, dry mouth, insomnia, diarrhea</td>
<td>(Cipriani et al. 2012, Peters et al. 2016)</td>
</tr>
<tr>
<td>Gamma-aminobutyric acid-A (GABA) receptor in brain</td>
<td>Inhibits activity of neurons</td>
<td>GABA channel opener: lorazepam and oxazepam</td>
<td>Can decrease verbally disruptive behavior</td>
<td>Drowsiness, confusion, dizziness, blurred vision, weakness</td>
<td>(Defrancesco et al. 2015).</td>
</tr>
<tr>
<td>Dopamine receptors</td>
<td>Receptors of dopamine</td>
<td>Dopamine receptor blocker: aripiprazole, clozapine, haloperidol, olanzapine, and quetiapine</td>
<td>Can decrease severe agitation, aggression , and psychosis in AD patients</td>
<td>Dry mouth, blurred vision, flushing, and constipation</td>
<td>(Herrmann &amp; Gauthier 2008)</td>
</tr>
</tbody>
</table>

*Table 3 examines different treatable symptoms of AD, the medications used to treat the symptoms, the mechanism by which the medication works, the outcomes of the medication use, and possible side effects from the medications.*
Figure 1. Age demographics of Alzheimer’s disease population in the year 2000 which represents 4.5 million people (Herbert et al. 2003) and the year 2010 which represents 4.7 million people diagnosed with AD (Herbert et al. 2013).
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