Alzheimer’s Disease: Overview and Treatment Options

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Introduction

Alzheimer’s disease (AD) is the most common cause of dementia in the United States affecting an estimated 5.4 million people, with over 60% of those diagnosed being women. Worldwide, an estimated 24.3 million, possibly as many as 35 million, people have been diagnosed with Alzheimer’s disease.\(^1\)\(^,\)\(^6\) It is estimated that by the year 2050 between 13 and 16 million Americans will be affected by AD.\(^2\)\(^,\)\(^3\) Alzheimer’s disease is more prevalent in African Americans and Hispanics than in whites.\(^1\) The majority of patients with AD are 65 years or older at the time of diagnosis, but about 5% of patients diagnosed with AD are under the age of 65. Patients who are diagnosed with AD between age 40 and 64 are considered to have early-onset AD.\(^2\) The incidence of AD increases exponentially with age.\(^1\)\(^,\)\(^2\)\(^,\)\(^5\) About 1 in 8 Americans age 65 and older are affected by AD and nearly half of Americans over age 85.\(^1\)\(^,\)\(^3\)\(^,\)\(^7\) AD reduces life expectancy with average survival after diagnosis being about 4 to 6 years.\(^1\)\(^,\)\(^2\)

Risk Factors and Genetics

The primary risk factor associated with AD is advancing age. Once a person turns 65 years old, his/her risk for AD doubles every five years.\(^6\)\(^,\)\(^7\) Other risk factors include head trauma, metabolic syndrome, diabetes, hypertension, and family history.\(^1\)\(^,\)\(^2\)\(^,\)\(^4\)\(^,\)\(^5\) There is growing evidence that supports a link between cardiovascular disease and its risk factors and the incidence of AD.\(^2\)\(^,\)\(^8\) Risk factors of cardiovascular disease that are also risk factors for AD are hypertension, high levels of low-density lipoprotein cholesterol (LDL), low levels of high-density lipoprotein cholesterol (HDL), obesity, atherosclerosis, and diabetes.\(^2\)\(^,\)\(^4\)\(^,\)\(^5\) Dysfunctional blood vessels in the brain may impair nutrient delivery to neurons and may reduce beta-amyloid (A\(\beta\)) clearance (see discussion below). Elevated levels of cholesterol in the brain may alter neuronal membrane functioning and contribute to neuritic plaque formation. Vascular disease may accelerate the deposition of A\(\beta\) in the walls of cerebral vasculature, which may contribute to neuronal toxicity. The rate of progression of dementia may be slowed by controlling hypertension. Diabetes may increase the risk of dementia through multiple mechanisms. Glucose metabolites may have a toxic effect on the brain, specifically structures of the hippocampus, and vasculature. Insulin itself may increase the risk of AD due to disturbances in insulin signaling pathways peripherally and in the brain.\(^2\)\(^,\)\(^5\) Insulin may also have a role in the regulation of metabolism of A\(\beta\) and tau protein.\(^7\)

Dominantly inherited forms of AD account for only a small percentage of cases; however, there is a definite genetic link.\(^1\)\(^,\)\(^2\)\(^,\)\(^5\) There is a high familial occurrence of AD linked to autosomal dominant traits on chromosomes 21, 14, and 1.\(^1\)\(^,\)\(^2\)\(^,\)\(^6\) Mutations on these chromosomes are associated with early-onset AD.\(^2\)\(^,\)\(^4\)\(^,\)\(^5\)\(^,\)\(^6\) Chromosome 21 contains a gene that encodes for amyloid precursor protein (APP). APP is a protein that is normally found throughout the body. Overproduction and/or transcription errors can lead to the production of an abnormal subunit of APP known as beta-amyloid peptide (A\(\beta\)).\(^1\)\(^,\)\(^2\) A\(\beta\) peptides consist of 36-43 amino acids. A\(\beta\) consisting of 42 amino acids is more neurotoxic that other amyloid forms and is prone to aggregate and form plaques.\(^1\)\(^,\)\(^2\)\(^,\)\(^4\)\(^,\)\(^5\) In fact, much of the neuronal damage associated with AD is caused by A\(\beta\). Chromosomes 1 and 14 are home to genes that code for proteins involved in APP processing. Defects in these genes are associated with the majority of cases of early-onset AD.\(^1\)\(^,\)\(^2\)\(^,\)\(^4\) Even though there is a definite link between certain genes and AD, the majority of cases of AD are considered to be sporadic.\(^1\)\(^,\)\(^2\)

Sporadic forms of AD may be linked to a susceptibility gene, APOE. APOE is found on chromosome 19 and encodes for apolipoprotein E (ApoE).\(^1\)\(^,\)\(^2\)\(^,\)\(^4\)\(^,\)\(^5\) ApoE is normally involved in cholesterol and phospholipid metabolism.\(^1\) ApoE is synthesized in the liver, cerebrospinal fluid, and central nervous system and acts as a transporter in the brain.\(^2\)\(^,\)\(^4\) ApoE is associated with increased A\(\beta\) deposition and it may also accelerate the progression of vascular dementia; it can bind neurofibrillary tangles (NFTs) as well.\(^2\)\(^,\)\(^5\)\(^,\)\(^6\)\(^,\)\(^8\) ApoE may also affect the rate of A\(\beta\)
clearance. The APOE gene occurs in three isoforms: *2, *3, and *4. APOE*4 is associated with an increased risk of late-onset AD. A person may have zero, one, or two APOE alleles; the more APOE*4 alleles present, the greater the risk of developing AD.

**Pathophysiology**

The most obvious findings in a brain affected by AD are atrophy and synapse loss; however, these features alone are not diagnostic because a certain amount of atrophy and synapse loss may occur with normal aging. Atrophy due to AD is mainly found in the temporal, parietal, and frontal lobes of the brain and synapse loss is most pronounced in the hippocampus. The main changes seen in the cerebral cortex of patients with AD are NFTs and neuritic plaques.

NFTs are most likely to form in large pyramidal neurons and, as such, are found primarily in the pyramidal regions of the neocortex, hippocampus, and amygdala. NFTs may also be found in the brainstem and locus ceruleus. Typically, NFT formation begins in the hippocampus and spreads to the neocortex. NFTs are composed of paired helical filaments containing abnormally phosphorylated tau protein. Tau protein normally provides structural support for microtubules in the cell, but cannot bind properly due to abnormal phosphorylation. The inability of tau protein to function normally results in cell death due to an abnormally functioning microtubule system. Severity of dementia is associated with the density of NFTs which are a sign of neuronal death.

Neuritic plaques are spherical bodies of tissue composed of granular deposits and the remnants of neuronal processes. Neuritic plaques have a three-tiered structure consisting of a central amyloid core, a middle region of swollen axons and dendrites, and an outer zone of degenerating neuritic processes. The amyloid core contains APP which can be cleaved to form neurotoxic Aβ. Neuritic plaques contain acute-phase inflammatory mediators due to local inflammation and neurodegeneration associated with Aβ deposition. Neuritic plaques also contain ApoE. Neuritic plaques may be found in patients without dementia, but plaques found in these patients do not contain abnormal proteins. The amount of amyloid deposition in neuritic plaques is related to the severity of neuronal damage; however, Aβ does not correlate with disease severity as strongly as does NFT density.

Neurotransmitters and enzymes are also affected by AD. Acetylcholine (ACh) is one of the main neurotransmitters affected by AD. Choline acetyltransferase levels are reduced by up to 90% in the cortical and hippocampal regions. The extent of reduction in choline acetyltransferase concentration is related to plaque density and disease severity. ACh and acetylcholinesterase concentrations are reduced in patients with AD. Muscarinic receptors in the cortex and hippocampus usually remain at normal or near-normal levels until late-disease. AD leads to a reduction in the number of nicotinic receptors in the brain. Cholinergic activity is most significantly altered by AD, but norepinephrine, serotonin, glutamate, and gamma-aminobutyric acid activity are also affected.

It has been proposed that oxidative stress, mitochondrial dysfunction, and postmenopausal loss of estrogen may have a role in the pathogenesis of AD. Oxidative stress and free-radical build-up may contribute to the development and progression of AD. Mitochondrial dysfunction disrupts neuronal energy metabolism and contributes to free radical accumulation, oxidative stress, and ultimately apoptosis. Estrogen is involved in neuronal growth and maintenance of normal cholinergic activity; it may also have antioxidant properties. Loss of estrogen due to menopause results in loss of the normal activities of estrogen in the brain. All three of these mechanisms may contribute to the pathogenesis of AD.

**Diagnosis and Staging**

Currently, a definitive diagnosis can only be made post-mortem, but advances in diagnostic technology have made clinical
diagnosis of AD up to 90% accurate when compared to post-mortem diagnosis.\textsuperscript{1,4} When making a clinical diagnosis, it is important to rule out other, potentially reversible, causes of impaired cognition. There are numerous medications and diseases that can negatively affect cognition (see Table 1).\textsuperscript{1,2,4,8,9} A thorough patient history is important because it documents symptoms and progression and it may indicate or help rule out potential causes of cognitive impairment.\textsuperscript{2,4,9} Neuropsychological testing may be performed, including a depression screening and in-depth assessment of the patient’s cognitive function.\textsuperscript{1,2,6,8}

Neuropsychological testing should be performed by a clinician that is trained to administer and interpret the results of the tests.\textsuperscript{1,6} Tests such as a mini-mental status examination, Blessed Dementia scale, Clinical Dementia Rating scale, Short Test of Mental Status, or other tests that assess cognitive function may also be performed.\textsuperscript{1,2,6,8} Tests that assess functional capacity, such as the Functional Activities Questionnaire, may also be beneficial.\textsuperscript{9} Brain scans are useful in determining the potential cause of impaired cognition and the extent of AD neuropathology. Magnetic Resonance Imaging (MRI) and computed tomography (CT) scans are the most commonly used methods for performing brain scans; however, there are other types of scans that may be used in addition to or instead of an MRI or CT scan.\textsuperscript{1,2,4,8} Certain biomarkers, such as Aβ and tau levels in cerebrospinal fluid, may also be measured to help diagnose a patient with AD.\textsuperscript{3,9,10} The goal of all these tests is to determine whether or not the patient meets the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria for dementia. Once a diagnosis of dementia is determined to be probable, the patient may be classified as having dementia of the Alzheimer’s type based on whether or not he/she meets criteria established by the National Institute of Neurological Disorders and Stroke, Alzheimer’s Disease and Related Disorders Association, American Academy of Neurology, or other reputable institution.\textsuperscript{1,2}

### Table 1: Factors that may cause symptoms of cognitive impairment

<table>
<thead>
<tr>
<th>Diseases that may affect cognitive function</th>
<th>Medications that may affect cognitive function</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adjustment disorder</td>
<td>• Anticholinergic agents</td>
</tr>
<tr>
<td>• Amnestic syndrome</td>
<td>• Anticonvulsants</td>
</tr>
<tr>
<td>• Delirium</td>
<td>• Antidepressants</td>
</tr>
<tr>
<td>• Depression</td>
<td>• Antihistamines</td>
</tr>
<tr>
<td>• Brain abscesses</td>
<td>• Antineoplastic agents</td>
</tr>
<tr>
<td>• Normal pressure hydrocephalus</td>
<td>• Antipsychotics</td>
</tr>
<tr>
<td>• Stroke</td>
<td>• Anti-arrhythmics</td>
</tr>
<tr>
<td>• Subdural hematoma</td>
<td>• Anti-hypertensives</td>
</tr>
<tr>
<td>• Tumor within the central nervous system</td>
<td>• Corticosteroids</td>
</tr>
<tr>
<td>• Cardiac arrhythmia</td>
<td>• H-2 receptor antagonists</td>
</tr>
<tr>
<td>• Heart failure</td>
<td>• Immunosuppressants</td>
</tr>
<tr>
<td>• Vascular occlusion</td>
<td>• Narcotic analgesics</td>
</tr>
<tr>
<td>• Vitamin B-12, folate, or iron deficiency</td>
<td>• NSAIDs</td>
</tr>
<tr>
<td>• Infections</td>
<td>• Sedative hypnotics</td>
</tr>
<tr>
<td>• Metabolic disorders</td>
<td>• Anxiolytics</td>
</tr>
<tr>
<td></td>
<td>• Skeletal muscle relaxants</td>
</tr>
</tbody>
</table>


Before treating AD, it is important to determine what stage of disease the patient is experiencing. There are two main scales used to determine the patient’s current state and their prognosis, the Global Deterioration Scale and the Clinical Dementia Rating Scale. Based on these rating scales, the patient’s stage can be determined and described, as can the patient’s prognosis based upon the current state of their dementia. The description of each stage of AD is based upon the patient’s current level of cognitive function and is defined in Table 2.\textsuperscript{1,2}
### Table 2: Stages of Cognitive Decline

<table>
<thead>
<tr>
<th>Stage of Cognitive Decline</th>
<th>Features/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Cognitive state remains normal; no change from normal</td>
</tr>
<tr>
<td>Very mild</td>
<td>Often forgetful; no clinical/objective decline noted</td>
</tr>
<tr>
<td>Mild</td>
<td>Worsening of patient’s condition is noted upon psychiatric testing; ability to maintain a job and social function are affected; patient may experience anxiety or denial about condition, but in a mild form</td>
</tr>
<tr>
<td>Moderate</td>
<td>Affect appears flat and patient may seem withdrawn; concentration ability and ability to perform complex tasks are diminishing</td>
</tr>
<tr>
<td>Moderate/Severe</td>
<td>Dementia begins to develop (early stages of the disease); interactions with others become troublesome for the patient; orientation to people or place begins to be diminished</td>
</tr>
<tr>
<td>Severe</td>
<td>Assistance performing normal daily activities (i.e. bathing, dressing, etc.) is needed; behavioral symptoms begin to manifest (i.e. agitation, delusions, aggressive behavior)</td>
</tr>
<tr>
<td>Very Severe</td>
<td>Thinking and motor skills are lost; ability to speak and communicate effectively is lost; urinary incontinence may develop; patient’s become totally dependent upon caretakers</td>
</tr>
</tbody>
</table>


### Goals of Therapy

Once the stage of the patient’s disease has been determined, a treatment plan can be formulated. The main initial goal of therapy for AD is to maintain the patient’s independence for as long as is possible. This is considered best for both the patient and the patient’s caregiver. For the patient, maintaining independence allows him/her to remain within familiar surroundings, as opposed to moving them to a facility or alternative site for care with surroundings that are unfamiliar to the patient and, consequently, to which he/she must adapt. Once this goal of therapy has been addressed, focus can then be placed on the therapeutic goals of treatment.1 The goals of therapy are as follows: treat symptoms and cognitive impairment; preserve the patient’s current level of cognition; effectively manage and treat psychiatric and behavioral complications; and provide appropriate education to the patient and their family/caregiver with particular focus placed on overall expectations for the time course of the illness, expectations for each therapy option employed (both pharmacologic and non-pharmacologic), and financial expectations of therapy.2

### Treatment

Treatment for AD is based upon well-established drug classes, investigational agents, and non-pharmacological recommendations. Pharmacological treatment is based around two primary classes of pharmacological agents, the cholinesterase inhibitors and the n-methyl-d-aspartate (NMDA) receptor inhibitors. Investigational agents include estrogen, anti-inflammatory agents, monoamine oxidase inhibitors (MAO-Is), herbal medications and vitamins, and cholesterol lowering medications. It should be noted that these patients often experience non-cognitive symptoms, including psychosis, inappropriate/aggressive behavior, and depression. For these symptoms,
Alzheimer’s patients often receive antipsychotic medications, antidepressants, and/or anticonvulsant medications. Non-pharmacologic recommendation range from proper patient and family education to avoiding of environmental triggers of symptoms.1,2

The mainstay of treatment for AD is the drug class of cholinesterase inhibitors.1,2 The cholinesterase inhibitors that are available for the treatment of Alzheimer’s are donepezil (Aricept®), rivastigmine (Exelon®), galantamine (Razadyne®), and tacrine (Cognex®). These medications are designed to increase cognitive functioning via enhancement of cholinergic activity. They accomplish this by increasing the availability of acetylcholine within the central nervous system (CNS) through inhibition of the breakdown of acetylcholine by various cholinesterases, both acetylcholinesterase (AchE) and butyrylcholinesterase (BchE).1,2,11-13

Tacrine was the first medication within this class developed for the treatment of AD.2 It is labeled for the treatment of mild to moderate states of Alzheimer’s dementia and gained approval in 1993.11-13 Tacrine inhibits both AchE and BchE within both the CNS and the periphery of the body in a reversible fashion.1,11-13 It is recommended to initially give as 10 mg doses four (4) times daily due to its low bioavailability.11 Tacrine, however, is limited by its adverse reaction profile, namely hepatotoxicity, which has rendered the use of the medication as a last option.1,12 The less severe adverse reactions possible with the use of this medication are primarily gastrointestinal related and include nausea, vomiting, and diarrhea (NVD); indigestion; loss of appetite; and myalgia. The more severe adverse reactions possible include elevations of liver aminotransaminase levels, hepatotoxicity, liver failure, bradycardia, heart block, and a lowering of the seizure threshold. It is broken down mainly by cytochrome (CYP) enzymes within the liver.1,11-13 Tacrine has been shown to lead to low levels of improvement in cognitive function with at least 12-24 weeks of therapy; however, as mentioned previously, due to the adverse effects caused by tacrine and the availability of newer agents with less severe adverse effects, tacrine is no longer commonly used.1,2,11-13

Donepezil (Aricept®), similar to tacrine, is indicated for the treatment of mild to moderate AD. However, unlike tacrine, it is also approved for the treatment of moderate to severe forms of the disease.1,2,6,11-13 It is more selective for its reversible inhibition of AchE than for BchE, and it also tends to be more specific for inhibition of the cholinesterases of the CNS and less for peripheral cholinesterases.1 Donepezil is given once daily in a dose of 5-10 mg, due to its high bioavailability and somewhat extended half-life. The adverse effect profile of this medication is mainly due to its effects on the cholinergic system within the body, and includes nausea, headache (HA), syncope, loss of appetite, insomnia, and vivid dreams, just to name a few. Serious adverse effects with the use of donepezil are rare, but include gastrointestinal (GI) hemorrhage, atrioventricular (AV) blockade, and Torsades de pointes.1,6,11-13 Donepezil is recommended to be given at bedtime to allow the patient to better tolerate the cholinergic adverse reactions. It is metabolized by CYP 3A4 isoenzymes and overall, it is well tolerated by most patients. Donepezil has been shown to produce improvements in cognitive function within 12-24 weeks of initiation of therapy, even in the case of adverse effects or a suspected loss of efficacy.1,14 These improvements can be seen for as long as two years in some cases. As mentioned previously donepezil is approved for the treatment of moderate to severe forms of AD, and, thus, is the only medication indicated for this stage of the disease.1

Rivastigmine (Exelon®) is another cholinesterase inhibitor that reversibly inhibits cholinesterase enzymes.1,2,6,11-13,15 It differs from tacrine in that it produces its cholinesterase inhibition primarily within the CNS, similar to donepezil. It is different from donepezil in that it inhibits both AchE and BchE, whereas donepezil is more selective for AchE.1 It is approved for the treatment of mild to moderate stage AD, but not for the moderate to severe stage of the disease.1,2,6,11-13 Rivastigmine is also different from all of the other cholinesterase inhibitors in that it comes in both oral dosage forms and a topical dosage form (extended release patch). It
is dosed initially at 1.5 mg given twice daily to be titrated by 1.5 mg/dose (3 mg/day) approximately every two weeks, not to exceed a maximum of 6 mg/dose (12 mg/day). Initial dosing for the patch is 4.6 mg (patch)/day to be increased to the 9.5 mg (patch)/day maintenance dose no earlier than four weeks after initiation. The maximum recommended daily dose for this dosage form is 9.5 mg/day.1,6,11-13 Similar to donepezil, the adverse effect profile of rivastigmine is much milder than that of tacrine. Mild adverse effects that may be seen include HA, dizziness, fatigue, and gastrointestinal effects (NVD, loss of appetite). Rivastigmine is the only cholinesterase inhibitor used for the treatment of AD which is not metabolized by CYP enzymes.1,2,6,11-13,15 It is metabolized by hydrolysis. As the adverse effects are most commonly seen when rivastigmine is taken on an empty stomach or when the rivastigmine dose is increased too rapidly, it is recommended that this medication be given with food.1

Galantamine (Razadyne®) is the final cholinesterase inhibitor used for the treatment of AD. It is indicated for the treatment of mild to moderate forms of AD. Similar to galantamine and tacrine, it is not indicated for the treatment of moderate to severe forms of the disease.1,2,6,11-13 It has a slightly different mechanism than that of the other cholinesterase inhibitors. In addition to reversibly inhibiting AchE mostly within the CNS, it also acts to activate nicotinic type receptors at a site different to that of which is stimulated by its cholinesterase activity. Hence, the stimulation of these nicotinic receptors does not require the presence of Ach or Bch.1,4,11-13 As was the case with donepezil and rivastigmine, galantamine has a mild adverse effect profile. The mild adverse effects associated with the use of galantamine are mainly associated with the cholinergic system including HA, bradycardia, and gastrointestinal effects (N/V/D). Galantamine is metabolized by multiple CYP isoenzymes. Galantamine is dosed two times daily, initially at a 4 mg dose.1,2,6,11-13 It is recommended that the dose of galantamine be titrated no sooner than every 4 to 6 weeks, maximum dose of 24 mg daily. Improvements in cognitive function have been seen with use of this medication.1,16

Memantine (Namenda®) is the only other medication, aside from donepezil, indicated for the treatment of moderate to severe AD; however, it does not fall into the class of the cholinesterase inhibitors. It antagonizes N-methyl-D-aspartate glutamate receptors. Glutamate within the CNS can cause excitotoxicity leading potentially to cell death. Since it has a different mechanism of action, it is commonly employed in a combination with a cholinesterase inhibitor. However, monotherapy with this agent may be just as effective as the combination with donepezil.17 It should be noted that this medication should not be used as monotherapy in a patient suffering from only mild to moderate forms of the disease.6 Generally, memantine is tolerated well by most patients.1 Due to having no effect on the cholinergic system, the adverse effect profile of memantine is milder than the cholinesterase inhibitors. The common adverse effects associated with the use of this medication include dizziness, constipation, and headache. The severe adverse effects that are possible with the use of memantine include cardiac failure, transient ischemic attack, deep vein thrombosis, seizure, liver failure, or acute renal failure. While most of these effects are very rare, the cardiovascular effects occur with the greatest frequency (about 1%).13 Memantine is initiated at 5 mg daily and titrated according to the following schedule: 5 mg daily initially for one week, then 15 mg daily divided into two doses, then 10 mg two times daily.1,6,11-13 Memantine has been shown to improve cognitive function, as well as reduce the overall responsibility of the patient’s caregiver.1

Alternative Therapies

There are various medications currently under investigation for the treatment of AD. Estrogen has been shown to increase blood flow within the cerebrum of the brain, allowing for better delivery of glucose and increase repair of damaged neurons. These may provide beneficial
Alzheimer’s Disease: Overview & Treatment Options

Effects for patients with AD. The benefits were first noticed in women taking hormone replacement therapy. A lower incidence of AD was noted in these women and lead to current investigation into their use for AD.\textsuperscript{1,2}

Monoamine oxidase inhibitors (MAO-Is) are another drug class under investigation for the treatment of AD as a result of the finding of high levels of MAO type B in patients with AD. Use of the MAO-B inhibitor, selegiline, has been shown to increase cognitive functioning in some trials.\textsuperscript{1} This, coupled with the fact that these agents can be used in the treatment of depression, has led to a promising investigation into the use of these medications for treatment of AD.\textsuperscript{1,2,11-13,18,19}

Cerebrolysin is a medication approved for the treatment of AD in various other countries, but not in the U.S. Made from purified human brain proteins and purified for use in humans, cerebrolysin can freely cross the blood brain barrier to exhibit its beneficial effects in Alzheimer’s patients, which include protective and supportive effects on neuronal function. This is thought to enhance cognitive function in these patients. Cerebrolysin may also have anti-inflammatory effects, may interact with GABA receptors, may interact with amyloid proteins, and may enhance the actions of some neuroprotective peptides. None of these mechanisms have been proven, nor are they well understood.\textsuperscript{20}

Non-steroidal anti-inflammatory drugs (NSAIDs) have also come under investigation for use as a potential treatment of AD. It is thought that inhibiting inflammation in the CNS could possibly lead to reduced formation of neuritic plaques, leaving the patient potentially with a better cognitive state. Clinical trials have only been able to establish a decreased risk of inflammation with use of these medications in Alzheimer’s patients, but there has been no improvement of cognitive symptoms shown with their use.\textsuperscript{1,2}

The herbal supplement, ginkgo biloba, is the only OTC product under investigation for improved cognitive function in patients with AD. Speculation for the use of this medication is based upon its potential ability to enhance the patient’s memory. Ginkgo biloba may exhibit antioxidant properties, and may also enhance cholinergic function in Alzheimer’s patients. While improvements in cognitive function appear promising, there is not enough evidence to fully support the use of ginkgo biloba for improvement in the patient’s Alzheimer’s condition.\textsuperscript{1,2}

Other agents currently under investigation for the treatment of AD include the 3-hydroxy-3-methyl-glutaryl coenzyme (HMG CoA) reductase inhibitors, also known as the statins; anti-amyloid beta monoclonal antibody agents; alpha and beta secretase inhibitors (i.e. rosiglitazone, semagacestat); valproate for a reduction of tau phosphorylation; and omega-3-fatty acids, to name a few.\textsuperscript{20} This is an active area of clinical investigation.

The final drug therapy options available for the treatment of AD focus more on the impact of AD on the patient’s daily life and common comorbid conditions. Many AD patients experience significant depression or anxiety. There are many drug classes involved with the specific treatment of each of these conditions.\textsuperscript{1,2}

Depression associated with AD is treated in a similar manner to clinical depression. The medication classes employed for the treatment of this type of depression include the selective serotonin reuptake inhibitors (SSRIs) (i.e. sertraline, fluoxetine), the serotonin-norepinephrine reuptake inhibitors (SNRIs) (i.e. venlafaxine, duloxetine), the norepinephrine reuptake inhibitors (i.e. bupropion), the tricyclic antidepressants (TCAs) (i.e. amitriptyline, desipramine), the tetracyclic drugs (i.e. mirtazapine), and the monoamine oxidase inhibitors (i.e. selegiline). For a more extensive discussion of the treatment of depression, refer to pharmacotherapeutic texts and the most up-to-date guidelines.\textsuperscript{1,2,18,19}

Anxiety is another condition that patients with AD may experience. This becomes more common as the patient’s cognitive function declines and their lack of memory leads them to experience anxiety. Like depression in AD, anxiety disorders in a patient with AD is treated much the same as in other patients. The
medication therapy employed for the treatment of this type of anxiety varies depending on the diagnosis, but treatment may include benzodiazepines (BDZs) (i.e. diazepam, lorazepam), buspirone, SSRIs (i.e. sertraline, fluoxetine), TCAs, venlafaxine, and others. The reader is referred to pharmacotherapeutic texts and the most up to date set of guidelines available.\textsuperscript{1,2,21,22}

**Prognosis**

AD follows a predictable course and may progress over a period of 10 or more years. Multiple areas of cognition are affected by AD.\textsuperscript{1,2} Initially, a patient may have vague complaints about memory impairment or family may consider the patient to be forgetful.\textsuperscript{2,9} Patients may also present with mild cognitive impairment (MCI), a condition in which cognitive impairment is present but not significant enough to diagnose dementia.\textsuperscript{2,6,9} MCI may be the initial manifestations of AD, but not all patients with MCI progress to AD.\textsuperscript{2,8} Rating scales may help to gauge patient deterioration. The global deterioration scale and clinical dementia rating scale are both appropriate tests for measuring deterioration of a patient’s disease.\textsuperscript{2} Patients should have cognitive function reassessed on a scheduled basis, possibly every 6 months, so that disease progression can be documented and therapy can be monitored closely to ensure appropriateness.\textsuperscript{2,6,9} As AD progresses, behavioral symptoms may appear and should be treated accordingly.\textsuperscript{2,6} Towards the later stages of AD, loss of daily function may occur and the patient will eventually get to a point where home care is not appropriate; a residential facility may be necessary in order for the patient to receive adequate care. Infections, specifically pneumonia, are the most common cause of death in patients with late-stage AD.\textsuperscript{1,2}

**Risk Reduction**

Over 5 million American are suffering from AD, and it is predicted that AD will affect as many as 16 million Americans by the year 2050.\textsuperscript{1} Currently, there are no proven strategies to prevent AD. Controlling risk factors for cardiovascular disease, such as blood pressure, cholesterol, and weight, especially in mid-life, may help reduce the risk of developing AD. Staying physically, mentally, and socially active may also help reduce the risk of developing AD. Physical activity may directly protect the brain by stimulating blood flow and oxygen delivery, and it also helps maintain cardiovascular health. The mechanism by which mental activity and social interaction may help reduce the risk for AD is unknown, but stimulation of the brain is thought to be beneficial.\textsuperscript{7,23} As head trauma is a risk factor for AD, wearing a helmet when riding a bicycle or participating in contact sports can help prevent head trauma. For older patients, carefully going through the home and removing possible tripping hazards can help prevent falls and related head trauma. Minimizing head trauma will not lower a patient’s risk for developing AD, but it can help keep a patient’s risk as low as possible.\textsuperscript{23} At the present time, there is no way to prevent AD; however, the above strategies may be beneficial in reducing risk.\textsuperscript{7,23}

**Conclusion**

AD causes degeneration of neurons in higher brain areas.\textsuperscript{1,2} The most significant consequence of AD is the loss of cortical and hippocampal neurons as synapse loss is associated with disease severity.\textsuperscript{1,5,10} NFTs and cell loss are centralized in the cerebral cortex and hippocampus.\textsuperscript{1,5,10} AD is also responsible for vast destruction of cholinergic pathways.\textsuperscript{1,2,5} The pathologic processes of AD may begin many years before symptoms are seen.\textsuperscript{1,2,6,8,10} Treatments such as the cholinesterase inhibitors and memantine may provide some relief from symptoms, but there is no cure for AD. Even with treatment, patients with AD will experience cognitive impairment that progressively worsens until death.\textsuperscript{1,2}
References:


