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Key Inforbits

- Introduction to Alzheimer's
- Clinical Presentation
- Diagnosis of Alzheimer's
- Nonpharmacological Therapy
- Pharmacological Therapy
- Future Therapies

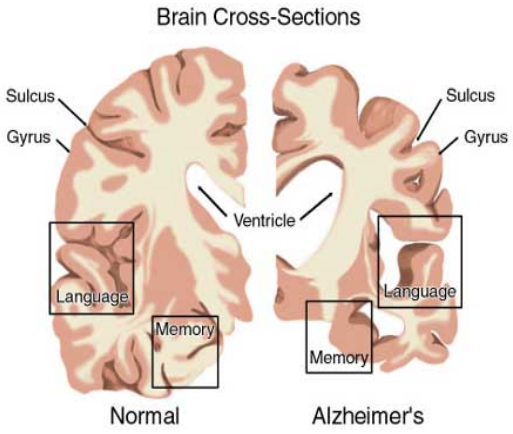
September is… World Alzheimer's Month

INTRODUCTION TO ALZHEIMER'S

Alzheimer's disease (AD) is a form of dementia that is characterized by irreversible neurodegeneration and affects roughly 5.4 million Americans as of 2011, making it the 6th leading cause of death in the United States. Roughly 50-60% of late-life cognitive dysfunction is caused by AD, and 96% of AD patients are over the age of 65. Advanced age is the leading risk factor for development of AD, and the prevalence of AD is projected to increase as our population continues to age.[1]

The burden of Alzheimer's disease is felt not only by the patient, but also by the family and the care providers of the patient. Most patients spend the majority of their diagnosis in the most severe state of their condition, which is characterized by the inability to perform everyday tasks such as speak, walk, self-feed, recognize family members, and others.[1,2]

The definitive cause of Alzheimer's disease is unknown; however, there are some risk factors for AD such as head trauma, diabetes, hypertension, advancing age, and family history. AD has been associated with autosomal-dominant traits on chromosomes 1, 14, and 21.[3] The presenilin-1 gene and the presenilin-2 gene are located on the chromosomes 14 and 1 respectively. Both of these chromosomes code for the inherited form of AD. Amyloid precursor protein (APP) is located on chromosome 21 and is responsible for the neuronal damage seen in AD. Most cases of AD are sporadic in nature; however, some of them have been linked to a susceptibility gene, Apolipoprotein E (ApoE). Due to an overproduction of transcription errors, beta-amyloid is produced. Beta-amyloid is an abnormal subunit that demonstrates a higher level of toxicity compared to other amyloid forms. These high levels of beta-amyloid are thought to be associated with the progression of AD. ApoE has three different alleles E2 (protective against AD), E3 (the most common), and E4 (increases the risk of AD).[4]



The brain atrophies due to the aging process. Therefore atrophy cannot be purely diagnostic for AD. However, the frontal, parietal and temporal lobes tend to atrophy in patients with AD. Patients with AD experience neuronal changes such as neurofibrillary tangles, neuritic plaques, amyloid angiopathy, and granulovacuolar degeneration. Along with these neuronal changes, patients with AD experience changes in neurotransmitters and enzymes. Decreased levels of acetylcholine, acetylcholinesterase and nicotinic receptor proteins are seen in patients with AD.[1,4]

Theories as to what causes AD[5]
Acceleration of Aging
Degeneration of anatomical pathways (e.g. cholinergic pathway)
Environmental Factors (e.g. head injury and malnutrition)
Genetic Factors
Vascular Factors
Metabolic Disorders
Immune System Dysfunction
Infectious Agents

The ingestion of certain types of food have been linked to potential causes of AD. Many theories suggest that soy consumption may be a contributor to AD. Soy has topoisomerase II poisons, genistein, and diadzin which can be very detrimental. Genistein has been shown to displace estrogen in the body, thus diminishing its effects. Estrogen has been shown to improve cognition and reduce potential risks of developing AD; however, evidence is weak. These anti-nutrients found in soy can lead to DNA replication damage and cerebral atrophy. In short, there is not just one causative agent of AD and this just further provides reason to evaluate and correct any and all potential causes of AD.[6,7,8]

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CLINICAL PRESENTATION

The symptoms of AD can be broken down into two different categories: cognitive or psychiatric. Cognitive symptoms are often referred to as the 4 A's: aphasia, apraxia, amnesia, and agnosia. Depression, personality changes, hallucinations and delusions are often associated with psychiatric symptoms. **Aphasia** is when a person loses their ability to communicate; Patients have trouble speaking, writing and understanding languages. **Apraxia** is just another way of saying that a person forgets how to do everyday activities. Some patients may forget all motor skills such as brushing their teeth, getting dressed, and walking. **Amnesia**, or memory loss, is probably the most common symptom shown in

patients with AD. Patients who experience amnesia often forget memories and information. Patients with **agnosia** lose the ability to interpret things like light or sound due to damage caused by AD.[1,2,3]

Several noncognitive symptoms also present with AD, and become more prevalent in the latter stages of the disease. Noncognitive symptoms typically include impairments in functional abilities (preparing meals, paying bills, transportation, using the restroom, etc.), depression, and behavioral disturbances.[4] One recent trial that evaluated over 2000 elderly patients without a diagnosis of dementia at enrollment compared patients that developed cognitive impairment over the course of the study to patients that did not develop cognitive impairment. The patients that developed cognitive impairment were more likely to develop depression and behavioral disturbance, which demonstrates the presence of noncognitive symptoms in the early stages of the disease as well.[5]

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DIAGNOSIS OF ALZHEIMER'S

Diagnosing Alzheimer's is very important to actually determine the cause of certain symptoms patients may be experiencing. About 10-30% of the population is incorrectly diagnosed with AD.[3] Multiple tests need to be performed in order to get an accurate diagnosis of AD. A medical history should be taken in order to determine if any medications or comorbid conditions could be the cause of symptoms. Physical and neurological examinations can also be done to help determine potential causes of AD. Mental exams like the Mini-mental-status exam (MMSE) can also be done to determine the severity or progression of AD. A MMSE score of 20-24 indicates mild AD, score of 13-20 indicates moderate AD, and a score of less than 12 indicates severe AD.[4]

Stages of Alzheimer's Disease[2]

Mild	Moderate	Severe
• Problems remembering recent events • Patient can still perform normal activities just at a declined level • Often become self-conscious of their declining abilities so they may withdraw from everyday activities and hobbies	• The ability to recall recent events is very impaired • Daily activities become more of a problem and patients may need help • Patients may forget certain things about their past • Psychiatric symptoms are common	• Requires 24 hour care • Patient is unable to take care of themselves • Need help doing everyday activities • Trouble eating, moving, and communicating

1. Brandt NJ and Williams BR. Geriatric Dementias. In: Koda-Kimble & Young Applied Therapeutics: The Clinical Use of Drugs. Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR, editors. 10th edition. New York: Wolters Kluwer Health; c2013; Chapter 103.
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DSM-5 criteria for either **probable** or **possible** Alzheimer's disease:[1]

Mild Neurocognitive Disorder	Major Neurocognitive Disorder
Probable Alzheimer's disease is diagnosed if an AD genetic mutation is discovered. **Possible Alzheimer's disease** is diagnosed if all three of the following are present without AD genetic mutation discovered:	**Probable Alzheimer's disease** is diagnosed if one of the following is discovered:
1. Decline in memory and learning 2. Progressive, gradual decline in cognition 3. No evidence of other neurological conditions/causes	1. Genetic mutation discovered from family history or genetic testing 2. All three of the following are met: a) Decline in memory, learning, and another cognitive domain b) Steadily progressive, gradual decline in cognition c) No evidence of other neurological conditions/causes

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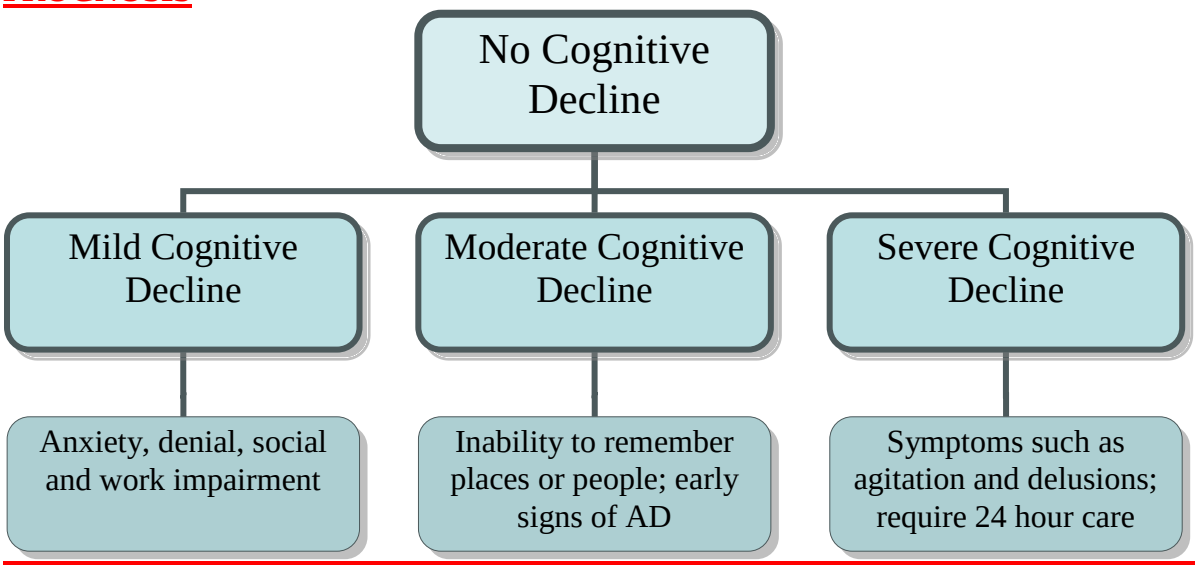
PROGNOSIS



1. Adapted from: Brandt NJ and Williams BR. Geriatric Dementias. In: Koda-Kimble & Young Applied Therapeutics: The Clinical Use of Drugs. Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR, editors. 10th edition. New York: Wolters Kluwer Health; c2013; Chapter 103.

NONPHARMACOLOGIC THERAPY

Caregivers and patients should be counseled on the available therapies, possible outcomes, and any quality of life issues. The main goal of nonpharmacologic therapy is to identify the triggers (environmental and personal discomforts), avoid triggers, and help redirect the patient's attention.[1,2]

Environmental Triggers	Personal Discomforts	Nonpharm Therapies
• Background distraction like a television • Glare • Loud noises	• Fears • Hunger or thirst • The need to urinate • Temperature changes	• Music and light therapy • Exercise • Aromatherapy

Considerations should also be given to anticipating and planning for the degeneration that is inevitable with the condition. A healthcare proxy should be established before the disease progresses to an advanced stage or an acute event occurs. A healthcare proxy is someone that ensures that the patient's wishes are carried out after the patient is unable to do so, and the proxy should be educated on the process of surrogate decision making. Better outcomes have been associated with the use of predefined patient wishes and a goal of care being established. The most common goal of therapy in the advanced stage is comfort, and Alzheimer's maintenance medications may not be appropriate if this is the goal of therapy.[3]

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3. Mitchell SL. Advanced Dementia. N Engl J Med. 2015;372:2533-40.

PHARMACOLOGICAL THERAPY

There are currently five drugs that have a FDA labeled indication to treat Alzheimer's disease. Three of these drugs are acetylcholinesterase inhibitors (AChEIs) such as donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®). These drugs are recommended in the mild to moderate stages of the disease, although donepezil and the rivastigmine patch formulation have indications for all stages.[1,2,3] According to the NICE guidelines, donepezil is recommended for mild-to-moderate AD; however, the package insert states that it is indicated for mild, moderate, and severe AD. In a double-blind, parallel-group, placebo-controlled study, 248 patients were given donepezil 5 mg a day for 30 days and then 10 mg after that or placebo. The primary endpoints of the trial were changes in severe impairment battery (SIB) and modified Alzheimer's Disease Cooperative Study (ADCS-ADL-severe). Patients treated with donepezil had better SIB and ADCS-ADL scores compared to patients treated with placebo. Donepezil was shown to improve cognition in patients with severe AD. In another trial, donepezil was used to manage patients with severe AD. The objective of the study was to evaluate the safety and efficacy of donepezil in this multicenter, double-blind, placebo-controlled trial. Over 300 patients were randomized to receive placebo or donepezil 10 mg daily for 24 weeks. SIB and Clinician's Interview-Based Impression of Change-Plus input (CIBIC-Plus) were primary objectives. Patients treated with donepezil had better SIB and CIBIC-Plus scores compared to patients treated with placebo; donepezil is a safe and effective option for patients with severe AD. These two trials were well conducted and were some of the most recent trials done evaluating the use of donepezil in severe AD. Although the NICE guidelines were updated in 2011, they may be considered "outdated" compared to the information found in these trials and the package insert.[2,4,5,6]

Another drug that has been approved for use in the treatment of AD is memantine (Namenda®), which works by blocking NMDA receptors, enhancing glutamate transmission, and thereby enhancing neurocognition. A combination product of memantine and donepezil (Namzaric®) is also labeled for AD as these medications can be given together during the more severe stages of the disease. According to NICE guidelines, there is not enough evidence to recommend giving memantine beyond 6 months or in mild disease.[2,3,7]

In August 2014, CBS news reported on a controversial tactic employed by the maker of Namenda®, Forest Laboratories. Forest laboratories stopped the manufacture of brand name Namenda® 6 months before the release of the generic form of immediate release memantine and began to release Namenda XR®, a brand name extended release formulation of memantine. Forest Laboratories said that they believed the once daily dosing to be more beneficial than the twice daily dosing of Namenda® immediate release; however, the company has been criticized for forcing patients to switch to an oral solution or extended release formulation until the generic form becomes available in order to encourage the use of their brand name products.[8] In addition to the questionable ethics of discontinuing the product early, a shortage of the Namenda XR® formulation occurred shortly after the decision to focus on the manufacture of this product.[9] The state of New York filed a suit against Actavis (parent company of Forest Laboratories), and the court decided in May 2015 that Forest Laboratories must continue to manufacture Namenda® until the trial concluded.[10]

Vitamin E is another therapy that has been evaluated for the treatment of dementias, but it has not shown to have a favorable safety and efficacy profile. Although animal studies have shown that vitamin E can slow nerve damage and delay mortality, human studies have not shown vitamin E to be an effective therapy in the treatment of neurodegeneration. Vitamin E has also shown an increased risk of death in high doses and has shown to increase the risk of heart failure in some clinical trials. The APA does not recommend the use of vitamin E for the treatment of Alzheimer's disease.[11,12]

Other medications are frequently given for the treatment of noncognitive symptoms of AD. These medications include antipsychotics, benzodiazepines, antidepressants, and anticonvulsants. Both typical and atypical antipsychotics have demonstrated efficacy in controlling psychotic and behavioral symptoms in patients with dementia, although guidelines state that their use beyond 8-12 weeks requires more study and side effect profile should be taken into account when tailoring the antipsychotic regimen to the specific patient.[11,12] A study conducted in roughly 400 patients with dementia that were randomized to either placebo or an atypical antipsychotic revealed that these antipsychotics were more effective than placebo at improving symptoms of psychosis associated with AD. The study also demonstrated that the efficacy of atypical antipsychotics was limited to patients that experienced a low rate of side effects, showing the importance of selecting an antipsychotic with a favorable side effect profile.[13]

Benzodiazepines (BDZs) and anticonvulsants have also been used for the treatment of mood disturbances with AD. Although BDZs have been shown to improve behavioral symptoms, antipsychotics have displayed a greater duration of action in treating these symptoms, and BDZs have not shown much benefit beyond 8 weeks of therapy. Efficacy of anticonvulsants in the treatment of behavioral symptoms has not been well-documented in clinical trials, and they are generally not recommended for treatment.[11]

Depressive symptoms of AD are typically treated with antidepressants, although significant evidence to support their efficacy is lacking. A trial that randomized roughly 300 AD patients to sertraline, mirtazapine, or placebo evaluated the efficacy of these antidepressants in the treatment of depression in AD. The trial did not show any significant benefits over placebo in improving depressive symptoms, which seems to display the lack of benefit from using antidepressants in AD.[14] Generally, SSRIs are recommended if the physician decides to treat the depression due to the more favorable safety profile of these medications.[11,12]

Summary of Medications[1,2,3,7,12]

Class	Agents (Brand Name)	Recommendations	Notable ADRs
Medications for Cognitive Symptoms			
Cholinesterase inhibitors	Donepezil (Aricept®) Rivastigmine (Exelon®) Galantamine (Razadyne®)	Mild to moderate AD	GI disturbance Headache Insomnia ↓ Appetite
NMDA receptor antagonists	Memantine (Namenda®)	Severe AD Moderate AD if AChEI is contraindicated	Dizziness Headache Confusion
Combination Drugs	Donepezil/memantine (Namzaric®)	Moderate to severe AD (indication)	See above
Medications for Noncognitive Symptoms			
Antipsychotics	Aripiprazole (Abilify®) Olanzapine (Zyprexa®) Quetiapine (Seroquel®) Haloperidol (Haldol ®) Risperidone (Risperdal®) Various others	Used for psychosis and disruptive behavior Demonstrated efficacy in AD patients	Movement disorder Metabolic changes Hyperprolactinemia Insomnia Drowsiness Headache

Benzodiazepines	Lorazepam (Ativan®) Diazepam (Valium®) Various others	Used for anxiety and disruptive behavior Not as efficacious as antipsychotics	Hypotension Drowsiness Dependence
Anticonvulsants	Valproate derivatives (Depakote®) Carbamazepine (Tegretol ®)	Used for agitation and aggression Not proven efficacious	GI disturbances Weight changes Headache Insomnia Dizziness
Antidepressants	Sertraline (Zoloft®) Citalopram (Celexa®) Mirtazapine (Remeron®) Duloxetine (Cymablta®) Various others	Used for depression in AD Not proven efficacious	GI disturbances Sedation/insomnia Weight changes Sexual effects

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FUTURE THERAPIES

One of the targets for future therapies is the reduction of the **accumulation of beta amyloid**, which is associated with the plaques seen in the brains of Alzheimer's patients. Some potential ways that drug therapy may be able to accomplish this is by inhibiting the enzymes that cleave APP to release beta amyloid, by increasing the clearance of beta amyloid using the immune system, and by preventing the aggregation of beta amyloid. Enzyme inhibitors have shown to have a negative side effect profile and have not yet proven efficacious, but there is still investigation into certain types of enzyme inhibitors that may be more promising. Vaccines and biologics have been under investigation to increase the clearance of beta amyloid, but they have not shown efficacy to date and have triggered encephalitis in some patients. A synthetic prostaglandin, tramiprosate, has been evaluated for reducing beta amyloid aggregation.[1,2] In a study that enrolled 1,052 patients with probable AD, tramiprostate was evaluated for improvement in symptoms of dementia.[3] The study demonstrated improvements in memory and language abilities, although the authors concluded that additional studies are needed. Metal chelating agents are currently being studied to reduce the aggregation of beta-amyloid as certain metals are known to aid in this process, although some researchers believe that this option may be more harmful than beneficial.[1,2]

Insulin has also been a promising target for pharmacotherapy as insulin modulates the concentration of beta amyloid in the central nervous system, and impairment in insulin production or activity has been associated with neurodegeneration. Drugs such as GLP-1 agonists and inhaled insulin are currently being studied and have so far displayed promising results.1 Inhaled insulin has been shown to improve verbal communication, and a pilot study done in patients with mild cognitive impairment and/or probable AD (n= 104) demonstrated some functional improvement in delayed story recall, Alzheimer's Disease Assessment Scale, and severity of dementia.[4,5] The pilot study was conducted over a 4 year period, and the authors of the study concluded that studies of longer duration are warranted.[5]

Another target for drug research includes **tau proteins**, which are associated with the neurofibrillary tangles associated with AD. Lithium, valproate, metformin, and selenium are all being studied for their ability to help prevent the degradation of tau proteins, and methylene blue is being studied for its ability to prevent tau aggregation.[1,2] Lansoprazole and astemizole may also reduce tau-tau interactions and may be seen in future studies.[2]

Inflammation is also a hopeful target for reducing the risk of AD. Anti-inflammatory medications such as NSAIDs, some statins, nutraceuticals, and others are being studied for the potential to lower symptoms of AD. Studies have not shown much efficacy of these medications at this time, but they may be more beneficial if given before symptoms of AD begin.[1,2] Like metal-chelating agents, some researchers believe that anti-inflammatory therapy may be more harmful than beneficial.[2] In conclusion, there are several different potential targets that could direct the therapy of AD in the future. Therapies that prevent beta amyloid accumulation, prevent tau degradation and aggregation, decrease neuroinflammation, and improve insulin signaling in the brain are all being studied and have shown mixed results in treatment. Although there is no conclusive evidence on any of these strategies, future studies should help elucidate the safety and efficacy of these therapies.

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The last "dose" …

"As you get older three things happen. The first is your memory goes, and I can't remember the other two."
–Sir Norman Wisdom [1915-2010, OBE, English actor and comedian]

An electronic bulletin of drug and health-related news highlights, a service of …
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