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Key Inforbits

- Introduction to Alzheimer's Disease
- Presentation of Alzheimer's Disease
- Diagnosis of Alzheimer's Disease
- Nonpharmacological Therapy
- Pharmacological Therapy
- Other Treatment Options



September 21 is World Alzheimer's Day



Introduction to Alzheimer's Disease

Approximately 5.3 million Americans have Alzheimer's disease (AD). However, prevalence is expected to increase to 13.2 million by the year 2050, as 1 in 5 people will be older than 65 years.^{1,4} AD is the fifth leading cause of death in the United States, and survival following diagnosis is an estimated 4-6 years. Causes of death include: sepsis, pneumonia, choking and aspiration, nutritional deficiencies, and trauma.^{1,4}

AD dementia is the most common form of dementia, accounting for 50-60% of dementia cases.² Increasing age is the greatest risk factor for developing AD, and most people are 65 years and older at diagnosis; however, 5% of cases are classified as early onset and appear as early as age 40.^{1,2,4} The exact cause of AD is unknown, but it likely involves genetic, environmental, and lifestyle factors.³ Most early onset cases involve a genetic component, specifically alterations and mutations on chromosomes 1, 14, or 21.¹ Late onset cases are primarily associated with the apolipoprotein E (apo E) gene.¹ Other factors that increase the risk of developing AD are those associated with vascular disease: hypercholesterolemia, hypertension, atherosclerosis, coronary heart disease, smoking, obesity, and diabetes.^{1,3}

AD pathology is characterized by neuritic plaques and neurofibrillary tangles (NFTs) that are the framework for lesions found in the cortical and temporal lobes of the brain.¹ Other common findings are cortical atrophy and degeneration of neurons and synapses.^{1,4} How these characteristics and lesions lead to the disease is uncertain.¹ There are several explanations proposed: Beta amyloid protein (β AP) aggregation and deposition, hyperphosphorylation of the tau protein, inflammatory processes, dysfunction of the neurovasculature, oxidative stress, and mitochondrial dysfunction.^{1,3}



There is no current cure for AD. It's progressive in nature and symptoms worsen over time.¹ Treatments available aim to improve quality of life and slow the worsening of symptoms.¹ Many hypotheses have been suggested, but no one mechanism appears to be responsible for the development of the disease. In each case, however, the features are the same: degeneration of neurons, accumulation of NFT's and plaques, destruction of the cholinergic system, and persistent dementia until death.^{1,3}

References:

1. Slattum PW, Swerdlow RH, Hill AM. In: Alzheimer's disease. In DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York: McGraw-Hill Medical; c2011. Pg. 947-61.
2. Alzheimer's and Dementia [Internet]. Chicago: Alzheimer's Association; c2012 [cited 2012 Aug 10]. Available from: http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp
3. Alzheimer's [Internet]. Bethesda: Alzheimer's Disease Education and Referral Center; c2012 [cited 2012 Aug 10]. Available from: <http://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-fact-sheet> [Management of Alzheimer's Disease \(AD\)](#)
4. Querfurth HW, LaFerla FM, et al. Alzheimer's Disease. *N Engl J Med* 2010;362: 329-44.

Presentation

A patient suffering from AD may begin to have memory complaints that are nonspecific in nature, or most often, a family member points out to a family physician that the patient is having problems with memory.¹ In moderate stages, patients may exhibit behavioral problems or disturbances. As the disease progresses, it is common for the patient to be unable to function in everyday activities, and mental processes such as attention, memory, talking, understanding speech, decision making, and problem solving may gradually decline over the course of the illness.¹

Symptoms ¹		
Cognitive	Non-cognitive	Functional
<ul style="list-style-type: none">• Memory Loss• Aphasia• Apraxia• Agnosia• Disorientation• Impaired executive function	<ul style="list-style-type: none">• Depression, psychotic symptoms (hallucinations and delusions)• Behavioral disturbances (aggression, wandering, uncooperativeness, motor hyperactivity, and repetitive mannerisms)	<ul style="list-style-type: none">• Inability to care for self (dressing, bathing, toileting, and eating)

Diagnosis

The original guidelines for the diagnosis of AD were developed in 1984, and it only addressed later stages of AD, when symptoms of dementia were already present.² Diagnosis was solely based on symptoms and was only confirmed at autopsy.¹ It was thought that if a patient exhibited symptoms of AD, then underlying pathology was already present; or in contrast, if a patient did not exhibit symptoms, no underlying pathology was present.² Advances in the understanding of AD called for the revision of the original diagnostic criteria, and new diagnostic guidelines were released in 2011.^{1,2} It is now believed that AD may cause brain changes long before symptoms appear, and appearance of symptoms does not always signify abnormal changes in the brain have occurred.²

The new guidelines cover three distinct stages of the disease: the preclinical phase, mild cognitive impairment, and Alzheimer's disease Dementia. The first two stages are largely meant for research purposes as more information is needed before it can be applied to general practice.²



It is thought that pathophysiological changes may take place in the brain before the emergence of symptoms, defined as the preclinical stage.^{1,4} Positive Emission Tomography (PET) and analysis of cerebrospinal fluid (CSF) can detect these changes in some patients, but the risk of progression to AD is not fully understood.⁴ Therefore, measurement of biomarkers in the preclinical stage is only approved for research purposes.⁴ Mild cognitive impairment is distinguished by noticeable symptoms of memory impairment, but not significant enough to affect a person's independence.^{1,5} Patients in this stage may or may not progress to Alzheimer's dementia. Research is still examining standardizing clinical biomarkers in this stage.⁵

AD dementia appears in the final stage and it is secondary to AD pathology.⁵ Based on the new guidelines, AD dementia is classified into 3 groups: (1) probable AD dementia, (2) possible AD dementia, and (3) possible or probable AD dementia with evidence of the pathophysiological process (intended for research purposes).³

Probable AD Dementia:³

- Slow onset (months to years)
- Clear-cut history of worsening of cognition (reported or observed)
- The initial and most prominent deficits recognized from a full history and examination include
 - Amnestic presentation - impairments in learning and inability to recall recent information
 - Nonamnestic presentation
 - Language presentation - impairment in word finding
 - Visuospatial presentation - impairment in spatial cognition, impaired face recognition and alexia
 - Impairment in reasoning, judgment, and problem solving

*Probable AD dementia should not be assumed if evidence of a concomitant cerebrovascular disease, dementia with Lewy bodies, or evidence of another neurological disease is related to the onset in the worsening of cognitive impairment.

Possible AD Dementia:³

- The patient meets the core clinical criteria in cognitive deficits mentioned in probable AD dementia, but the onset is sudden or there is not enough historical detail or documentation of decline.
- The patient meets the core clinical criteria in cognitive deficits mentioned in probable AD dementia, but there is evidence of concomitant cerebrovascular disease, dementia with Lewy bodies, or evidence of another neurological disease that could have an effect on cognition.

References:

1. Slattum PW, Swerdlow RH, Hill AM. Alzheimer's Disease. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: A pathophysiologic approach*. 8th ed. New York: McGraw-Hill Medical; c2011. p. 947-59
2. Jack CR, Albert MS, Knopman DS, McKhann GM, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7: 257-262.
3. McKhann GM, Knopman DS, Chertkow H, Hyman BT, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:263-269.
4. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7:1-13.
5. Albert MS, DeKosky ST, Dickson D, Dubois B, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7:260-279.

Management of Alzheimer's Disease

There is no treatment available that has been proven to cure AD, terminate or reverse the disease course, or prolong life of the patient. Therefore, the goal of treatment is to manage cognitive symptoms and preserve functioning as long as possible while treating secondary psychiatric and behavioral symptoms as needed.¹

Nonpharmacological therapy

Nonpharmacological therapy is considered the primary intervention for AD. Behavioral management can be extremely beneficial and should be considered over medication when appropriate for symptoms such as sleep disturbances, agitation, aggression, urinary incontinence, wandering, as well as many others.¹

1. Identify symptoms
2. Identify cause of symptoms
3. Modify environment to eliminate triggers
ex: Noise, glare, personal discomfort (hunger/thirst, pain, constipation, infection, frustration), multiple distractions

Communication, education, and planning with the caregiver and with the patient, when appropriate, is key to successful management of this disease.¹

Pharmacological Therapy

Mild to moderate cognitive symptoms:

- Cholinesterase inhibitors have been proven to provide modest benefit early in disease course.¹

	Donepezil (Aricept®)	Rivastigmine (Exelon®)	Galantamine (Razadyne®)
Generic availability	YES ²	YES (Capsule only) ²	YES ²
Formulations¹	ODT	Capsule, Oral solution, Patch	Tablet, Oral solution, ER Capsule
Initial Dose¹	5mg QD in evening	1.5 mg BID 4.6 mg/day patch	4 mg BID 8 mg QD (ER)
Maintenance Dose¹	5-10 mg QD 23 mg QD (Mod-Severe)	3-6 mg BID 9.5 mg/day patch	8-12 mg BID 16-24 mg QD (ER)
Food¹	With or without food	With meals	With meals
Indication^{1,3}	Mild/Moderate/Severe	Mild/Moderate	Mild/Moderate

- Titrate to maintenance dose as tolerated. May experience mild to moderate gastrointestinal symptoms such as nausea, vomiting, and diarrhea, as well as urinary incontinence, muscle weakness, salivation, and sweating. All are considered equally effective and you may switch to another agent if no benefit is seen.^{1,3}
- Tacrine (Cognex®) was the first cholinesterase inhibitor approved for AD in 1993, but it is not commonly prescribed anymore due to significant side effects, including possible liver damage.³

Moderate to severe cognitive symptoms:

- Memantine, an antiglutamatergic agent, is indicated only in moderate to severe AD. This medication may be used alone but may show additional benefit when used in combination with cholinesterase inhibitors.¹

	Memantine (Namenda®)
Generic availability	NO ²
Formulations¹	Tablet, Oral solution
Initial Dose¹	5 mg QD
Maintenance Dose¹	10 mg BID
Food¹	With or without food
Indication¹	Moderate/Severe

- Memantine is considered well tolerated but may cause constipation, confusion, dizziness, headaches, hallucinations, coughing, or hypertension. Titrate weekly by 5 mg per day until maintenance dose is reached. Only titrate up to 10 mg QD in renally impaired patients.^{1,3}

Non-cognitive symptoms¹:

1. **Psychotic symptoms** (Hallucinations, delusions, suspiciousness)
 - Antipsychotics
2. **Inappropriate/Disruptive behavior:** (Agitation, aggression)
 - Antipsychotics
 - Anticonvulsants
3. **Depression:** (Poor appetite, insomnia, hopelessness, anhedonia, withdrawal, suicidal thoughts, anxiety)
 - Antidepressants



Other treatment options:

- **Estrogen:** Some evidence shows a lower incidence in estrogen therapy postmenopause; no evidence to support use as prevention or treatment
- **Antiinflammatory agents:** Lack of compelling data and significant incidence of adverse effects
 - NSAIDs: No cognitive benefit in AD or risk outweighs the benefit
 - Prednisone: Associated with worsening behavioral symptoms
- **Lipid lowering agents:** More research needed, reserved for patients with other indications for their use¹
- **Dietary Supplements:**
 - **Vitamin E:** Not recommended, conflicting evidence on benefit and associated with significant risk; high-dose may increase mortality
 - **Ginkgo biloba:** Not currently recommended; limited evidence of positive effect, significant drug interactions, and poorly standardized content of herbal products
 - **Huperzine:** Not currently recommended; possible benefit but more studies need to determine role in therapy and side effects associated
 - **Omega 3-Fatty Acids:** No evidence to prove benefit
 - **Axona (AC1202):** FDA gave permission in 2009 to market as a medical food based on trials and relatively safe adverse event profile¹. Further trials are planned to study safety/efficacy.⁴

References:

1. Slattum PW, Swerdlow RH, Hill AM. Alzheimer's Disease. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiologic approach. 8th ed. New York: McGraw-Hill Medical; c2011. p. 947-59
2. Donepezil, Galantamine, Memantine, Rivastigmine. In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Lexi-Comp, Inc. [updated 2012 Aug 14, cited 2012 Aug 12]. [about 30 p.]. Available from <http://online.lexi.com/crlsql/servlet/crlonline>
3. FDA-Approved Treatments for Alzheimer's. [Internet] Alzheimer's Association. c2012; 2012 Jan [cited 2012 Aug 15]; [about 3 screens]. Available from: http://www.alz.org/national/documents/topicsheet_treatments.pdf
4. A Positron Emission Tomography (PET) Study Evaluating Brain Metabolism of a Medical Food in Alzheimer's disease (AD): [Internet]. ClinicalTrials.gov; 2011 Oct 21 [cited 2012 Aug 15]; [about 4 screens]. Available from: <http://clinicaltrials.gov/ct2/show/NCT01122329?term=AC+1202&rank=1>



The last "dose" ...

"Alzheimer's is the cleverest thief, because she not only steals from you, but she steals the very thing you need to remember what's been stolen."

~ Jarod Kintz, *This Book Has No Title*

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