

Alzheimer's Disease: An In-Depth Review

Two (2.0) contact hours

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Purpose and Objectives

The purpose of this two contact hour CE course for healthcare professionals is to provide an overview of Alzheimer's disease (AD), its causes, diagnosis, latest management guidelines and therapeutic interventions.

After successful completion of this course, the learner will be able to:

1. Define Alzheimer's disease.
2. Discuss the prevalence of the disease.
3. Identify modifiable and non-modifiable risk factors for Alzheimer's disease.
4. Describe how Alzheimer's disease is diagnosed.
5. List two revised criteria in the *2011 Guidelines for Diagnosing Alzheimer's Disease*.
6. Identify two current FDA-approved medications used for the management of Alzheimer's disease.

Definition of Alzheimer's

Alzheimer's disease (AD) is a progressive, degenerative disorder that attacks the brain's nerve cells, or neurons, resulting in loss of memory, thinking and language skills, and behavioral changes.

AD is the most common cause of dementia, or loss of intellectual function, among people aged 65 and older.

It is **NOT** a normal part of aging.

National Institute on Aging [NIA], 2014.

Neurological Changes in AD

Researchers have found specific anatomical changes in the postmortem examination of the brain of people who suffered from AD, particularly in the neurons of the brain. These neurons, which produce the neurotransmitter, acetylcholine, break connections with other nerve cells and ultimately die. For example, short-term memory fails when Alzheimer's disease first destroys nerve cells in the hippocampus, and language skills and judgment decline when neurons die in the cerebral cortex.

Two types of abnormal lesions clog the brains of individuals with Alzheimer's disease:

- **Beta-amyloid plaques:** Sticky clumps of protein fragments and cellular material that form outside and around neurons.

- **Neurofibrillary tangles (Tau tangles):** Insoluble twisted fibers composed largely of the protein tau that build up inside nerve cells. Although these structures are hallmarks of the disease, scientists are unclear whether they cause it or a byproduct of it.

Neurological Changes in AD

Plaques and tangles in the brain are two of the main features of Alzheimer's disease. The third is the loss of connections between nerve cells (neurons) in the brain.

Neurological Changes in AD

Did you know?

The origin of the term Alzheimer's disease dates back to 1906 when Dr. Alois Alzheimer, a German physician, presented a case history of a 51-year-old woman who suffered from a rare brain disorder. A brain autopsy identified the plaques and tangles that today characterize Alzheimer's disease.

Test Yourself

Beta-amyloid plaques are:

- A. Protein fibers that build up inside nerve cells.
- B. Clumps of protein that forms outside of neurons.
- C. Insoluble protein bands found both inside and outside of cells

The correct answer is: B. Beta-amyloid plaques are sticky clumps of protein fragments and cellular material that form outside and around neurons.

Changes in Brain Anatomy and Physiology

Although we still don't know how the Alzheimer's disease process begins, it seems likely that damage to the brain starts a decade or more before problems become evident.

Changes in Brain Anatomy and Physiology

During the preclinical stage of AD, people are free of symptoms, but toxic changes are still occurring in the brain. As mentioned previously, beta-amyloid plaques can accumulate outside neurons, and neurofibrillary protein tangles can form inside neurons. These changes begin to cause the failure of information transfer at synapses. As a result, the total number of synapses declines, and neurons eventually die (Alzheimer's Association, 2014).

By the final stage of Alzheimer's, damage is widespread, and brain tissue has shrunk significantly (Vaughn, 2011).

The brains of people with advanced Alzheimer's show dramatic shrinkage from cell loss and widespread debris from dead and dying neurons.

Progression of Neurological Degeneration

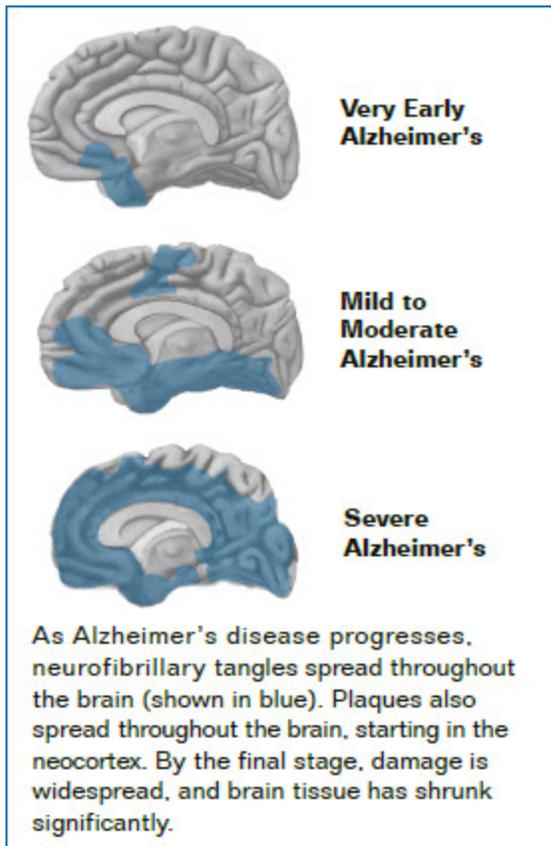


Image provided courtesy of NIH, 2014

Inside the Brain: Unraveling the Mystery of AD

This 4-minute captioned video shows the intricate mechanisms involved in the progression of Alzheimer's disease in the brain.

[Click here](#) **to view the video.**

<http://www.nia.nih.gov/alzheimers/alzheimers-disease-video>

What is Dementia?

Dementia is the loss of cognitive functioning (thinking, remembering, and reasoning, and behavioral abilities) to such an extent that it interferes with a person's daily life and functional ability. Dementia ranges in severity from the mildest stage, when it is just beginning to affect a person's functioning, to the most severe stage, when the person must depend completely on others for basic activities of daily living (Alzheimer's Foundation, 2014).

Many conditions and diseases cause dementia. Two of the most common causes of dementia in older people are Alzheimer's disease and vascular dementia, which is caused by a series of strokes or changes in the brain's blood supply.

Other conditions that may cause memory loss or dementia include:

- Medication side effects
- Chronic alcoholism
- Tumors or infections in the brain
- Blood clots in the brain
- Vitamin B12 deficiency
- Some thyroid, kidney, or liver disorders

Emotional problems, such as anxiety or depression, can make a person more forgetful and can be mistaken for dementia. For instance, someone who has recently retired or who is coping with the death of a spouse may feel sad, lonely and worried. Trying to deal with these life changes leaves some people confused or forgetful (Alzheimer's Foundation, 2014).

Dementia Versus AD

What is the difference between dementia and AD?

Dementia is the umbrella term for brain disorders that cause a person to lose their ability to function normally in daily life. Alzheimer's disease is the most common, but there are other dementias, such as vascular, Lewy body, etc.

Although we know Alzheimer's dementia is distinct from these other forms, in the early stages it may be difficult to differentiate among them. Additionally, many older people may have more than one condition, such as Alzheimer's disease combined with vascular disease and sometimes small strokes (Alzheimer's Foundation, 2014).

Prevalence

It is estimated that as many as 5.1 million Americans may have AD, which equates to approximately one in nine older Americans (Alzheimer's Association, 2014).

Of the 5 million people age 65 and older with Alzheimer's in the United States, 3.2 million are women and 1.8 million are men (Hebert et al., 2013 in Alzheimer's Association, 2014). More women than men have Alzheimer's disease and other dementias. Almost two-thirds of Americans with Alzheimer's are women (Hebert et al., 2013 in Alzheimer's Association, 2014).

Prevalence

Did you know?

The observation that more women than men have AD and other dementias is primarily explained by the fact that women live longer, on average, than men, and older age is the greatest risk factor for Alzheimer's (Seshadri et al., 1997 in Alzheimer's Association, 2014).

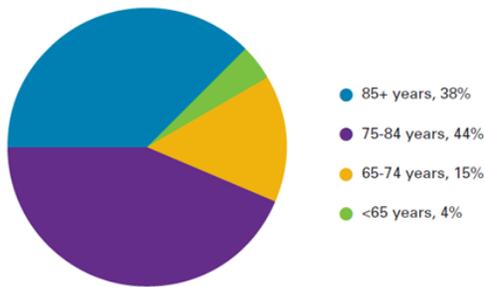
AD by Age

As our population ages, the disease impacts a greater percentage of Americans. The number of people age 65 and older will more than double between 2010 and 2050 to 88.5 million or 20 percent

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of the population; likewise, those 85 and older will rise three-fold, to 19 million, according to the U.S. Census Bureau (Alzheimer's Association, 2014b).

figure 1 Proportion of People With Alzheimer's Disease in the United States by Age



Percentages may not total 100 because of rounding.
Created from data from Hebert et al.¹¹⁴, A3

Image courtesy of Alzheimer's Association, 2014b.

The incidence of the disease is rising in line with the aging population.

Test Yourself

Which of the following statements are true regarding the incidence of AD in the United States?

- A. AD affects more men than women.
- B. AD is most prevalent in individuals older than 85 years of age.
- C. AD is most prevalent in individuals between the ages of 75-84 years.

The correct answer is: C. AD is most prevalent in individuals between the ages of 75-84 years.

AD affects 44% of Americans between the ages of 75-84 years of age, and only 38% of Americans over the age of 85. More women than men have Alzheimer's disease and other dementias.

Life Expectancy

Alzheimer's disease typically progress over 2 to 20 years, and individuals live on average for 8 to 10 years from diagnosis (NIA, 2014).

Individuals with Alzheimer's disease are likely to develop co-existing illnesses and most commonly die from pneumonia (Alzheimer's Association, 2014).

Alzheimer's disease is among the top 10 leading causes of death in the U.S (Alzheimer's Foundation, 2014).

Cost

The national tab for caring for individuals with AD is estimated at \$100 billion annually (Alzheimer's Foundation, 2014).

According to the Alzheimer's Foundation, AD costs U.S. businesses more than \$60 billion a year,

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stemming from lost productivity and absenteeism by primary caregivers, and insurance costs.

The annual cost of caring for one individual with Alzheimer's disease ranges from nearly \$18,500 to more than \$36,000, depending on the stage of the disease (Alzheimer's Association, 2014).

Types of Disease Processes

There are two types of the disease:

- Sporadic Alzheimer's disease
- Familial Alzheimer's disease (FAD)

Unlike sporadic Alzheimer's disease, FAD follows an obvious inheritance pattern. Less than 10% of Alzheimer's disease cases are FAD (Alzheimer's Association, 2014). This rare form of Alzheimer's disease usually occurs between the ages of 30 and 60.

The Continuum of AD

The brain changes of Alzheimer's may begin 20 or more years (Villemagne et al., 2013 in Alzheimer's Association, 2014) before symptoms appear. The time between the initial brain changes of Alzheimer's and the symptoms of advanced Alzheimer's is considered by scientists to represent the "continuum" of Alzheimer's.

At the start of the continuum, the individual is able to function normally despite these brain changes. Further along the continuum, the brain can no longer compensate for the neuronal damage that has occurred, and the individual shows subtle decline in cognitive function. Later, the damage to and death of neurons is so significant that the individual shows obvious cognitive decline, including symptoms such as memory loss or confusion as to time or place. Later still, basic bodily functions such as swallowing are impaired.

Risk Factors for AD

The exact causes of Alzheimer's disease are still unknown.

Current research indicates that Alzheimer's disease may be triggered by a multitude of factors, including age, genetic makeup, oxidative damage to neurons from the overproduction of toxic free radicals, serious head injuries, brain inflammation, and environmental factors (Alzheimer's Association, 2014).

Age:

Advancing age is the greatest known risk factor for AD. Although AD is not a normal part of aging, the risk of developing the illness rises with advanced age. Current research from the National Institute on Aging indicates that the prevalence of AD doubles every five years beyond age 65 (NIA, 2014).

Risk Factors for AD

Genetic Mutations:

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A small percentage of Alzheimer's cases, an estimated 1 percent or less, develop as a result of mutations in any of three genes (Bekris et al, 2010 in Alzheimer's Association, 2014). Scientists have identified three mutations on chromosomes 1, 14 and 21 that cause early-onset Alzheimer's disease, which generally affects those aged 30 to 60.

Note! A genetic mutation is an abnormal change in the sequence of chemical pairs that make up genes.

Other genes boost susceptibility, but do not signal that a person will definitely develop the disease. Multiple research studies indicate that inheritance of a specific one of the three forms, or alleles, of the apolipoprotein E (apoE) gene on chromosome 19 heightens the risk of late-onset Alzheimer's disease. Those who carry one copy of the allele e4 face a higher risk of developing Alzheimer's disease, and those with two copies of e4 confront the greatest risk.

Another relatively rare apoE allele, e2, appears linked to a lower risk of the disease (Alzheimer's Association, 2014).

Several other studies suggest that a gene or genes on chromosome 10 may also boost an individual's risk of developing late-onset Alzheimer's disease.

Risk Factors for AD

Did you know?

Inheriting any of these genetic mutations guarantees that an individual will develop Alzheimer's disease. In such individuals, disease symptoms tend to develop before age 65, sometimes as early as age 30, while the vast majority of individuals with Alzheimer's have late-onset disease, occurring at age 65 or later.

Test Yourself

Which of the following statements is correct:

- A. The risk for developing early-onset AD depends on the inheritance of mutations on chromosomes 1, 14 and 21.
- B. The risk for developing early-onset AD depends on the inheritance of a specific alleles of the apolipoprotein E gene on chromosome 19.
- C. The risk for developing early-onset AD depends on the inheritance of a mutation in one or more genes on chromosome 10.

The correct answer is: A. The risk for developing early-onset AD depends on the inheritance of mutations on chromosomes 1, 14 and 21.

Early-onset AD is related to mutations on chromosomes 1, 14 & 21. Late-onset AD is related to the inheritance of a specific alleles of the apolipoprotein E gene on chromosome 19 and the inheritance of a mutation in one or more genes on chromosome 10.

Modifiable Risk Factors

Research has shown that social and cognitive isolation are the two greatest modifiable risk factors for Alzheimer's disease.

Remaining socially and cognitively active may help build cognitive reserve, but the exact mechanism

by which this may occur is unknown. More research is needed to better understand how social and cognitive engagement may affect biological processes to reduce risk.

Low level of education:

People with fewer years of formal education are at higher risk for Alzheimer's and other dementias than those with more years of formal education (Fitzpatrick et al., 2004 in Alzheimer's Association, 2014). Some researchers believe that having more years of education builds a "cognitive reserve" that enables individuals to better compensate for changes in the brain that could result in symptoms of Alzheimer's or another dementia (Fitzpatrick et al., 2004 in Alzheimer's Association, 2014).

According to the cognitive reserve hypothesis, having more years of education increases the connections between neurons in the brain and enables the brain to compensate for the early brain changes of Alzheimer's by using alternate routes of neuron-to-neuron communication to complete a cognitive task. However, some scientists believe that the increased risk of dementia among those with lower educational attainment may be explained by other factors common to people in lower socioeconomic groups, such as increased risk for disease in general and less access to medical care (McDowell, 2007 in Alzheimer's Association, 2014).

Risk Factors for AD

Traumatic Brain Injury (TBI):

Moderate and severe TBI increase the risk of developing Alzheimer's disease and other dementias (Lye & Shores, 2000 in Alzheimer's Association, 2014). TBI is the disruption of normal brain function caused by a blow or jolt to the head or penetration of the skull by a foreign object (NIH, 2014). Not all blows or jolts to the head disrupt brain function.

Moderate TBI is defined as a head injury resulting in loss of consciousness or post-traumatic amnesia that lasts more than 30 minutes. If loss of consciousness or post-traumatic amnesia lasts more than 24 hours, the injury is considered severe. Half of all moderate and severe TBIs are caused by motor vehicle accidents (NIH, 2014). Moderate TBI is associated with twice the risk of developing Alzheimer's and other dementias compared with no head injuries, and severe TBI is associated with 4.5 times the risk (Plassman et al., 2000 in Alzheimer's Association, 2014).

Groups that experience repeated head injuries, such as boxers, football players and combat veterans, are at higher risk of dementia, cognitive impairment and neurodegenerative disease than individuals who experience no head injury. Evidence suggests that even repeated mild TBI might promote neurodegenerative disease (Omalu, 2005 in Alzheimer's Disease, 2014). Some of these neurodegenerative diseases, such as chronic traumatic encephalopathy, can only be distinguished from Alzheimer's upon autopsy.

Test Yourself

Which of the following options best describes a modifiable risk factor for AD?

- A. Traumatic Brain Injury (TBI)
- B. Limited formal education
- C. Active and engaging social interactions

The correct answer is: B. Limited formal education.

TBI is a NON-modifiable condition. Active and engaging social interactions is not a risk factor for AD, but rather a protective mechanism against the development of AD.

Warning Signs

Although every case of Alzheimer's disease is different, experts have identified common warning signs of the brain disease. Remember, Alzheimer's disease is not a normal part of aging, and it is important to look for signs that might indicate Alzheimer's disease versus basic forgetfulness or other conditions.

With Alzheimer's disease, these symptoms gradually increase and become more persistent.

Warning Signs

If someone is exhibiting these symptoms, the person should check out his or her concerns with a healthcare professional. Awareness of these warning signs is not a substitute for a consultation with a healthcare professional.

Typical warning signs include:

- Memory loss, especially of recent events, names, placement of objects, and other new information
- Confusion about time and place
- Struggling to complete familiar actions, such as brushing teeth or getting dressed
- Trouble finding the appropriate words, completing sentences, and following directions and conversations
- Poor judgment when making decisions
- Changes in mood and personality, such as increased suspicion, rapid and persistent mood swings, withdrawal, and disinterest in usual activities
- Difficulty with complex mental assignments, such as balancing a checkbook or other tasks involving numbers

(Alzheimer's Foundation, 2014)

Diagnosis

A definitive diagnosis of Alzheimer's disease can be made only through autopsy after death, by linking clinical measures with an examination of brain tissue. However, there are several methods and tools available to distinguish between "possible Alzheimer's disease" (symptoms may be due to another cause), "probable Alzheimer's disease" (no other cause for the symptoms can be found), or some other disease (Alzheimer's Foundation, 2014).

Clinicians can diagnose "probable" Alzheimer's disease by:

- Taking a complete medical history in which overall health, past medical problems, ability to carry out daily activities, and changes in behavior and personality are reviewed.
- Conducting tests of memory, problem solving, attention, counting, and language.
- Carrying out standard medical tests, such as blood and urine tests, to identify other possible causes of the problem.
- Performing brain scans, such as computed tomography (CT) or magnetic resonance imaging (MRI), to distinguish Alzheimer's from other possible causes for symptoms.

These tests may be repeated over time to provide information about how the patient's health and memory are changing. Tests can also help diagnose other causes of memory problems, such as mild cognitive impairment and vascular dementia.

Note! Proper diagnosis is critical since there are dozens of other causes of memory problems. Some memory problems can be readily treated, such as those caused by vitamin deficiencies or thyroid problems. Other memory problems might result from causes that are not currently reversible, such as AD.

The sooner an accurate diagnosis of "probable" Alzheimer's disease is made, the easier it is to manage symptoms and plan for the future.

Revised Guidelines

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association proposed revised criteria and guidelines for diagnosing Alzheimer's disease. These criteria and guidelines updated diagnostic criteria and guidelines published in 1984 by the Alzheimer's Association and the National Institute of Neurological Disorders and Stroke.

In 2012, the NIA and the Alzheimer's Association also proposed new guidelines to help pathologists describe and categorize the brain changes associated with Alzheimer's disease and other dementias.

The 2011 Guidelines for Diagnosing Alzheimer's Disease released by the National Institute on Aging and the Alzheimer's Foundation ask clinicians to look beyond just memory loss for additional symptoms that may mark onset of the disorder, such as problems with judgment.

In addition, the revised guidelines outline ways the healthcare provider should approach evaluating the causes and progression of cognitive decline. For example, healthcare providers are made aware that mild cognitive impairment (MCI) may in many cases progress to Alzheimer's disease and that memory impairment is not always the first symptom of Alzheimer's (Bernard, 2011).

Differences between the Original and New Criteria

The 1984 diagnostic criteria and guidelines were based chiefly on a physician's clinical judgment about the cause of an individual's symptoms, taking into account reports from the individual, family members and friends; results of cognitive tests; and general neurological assessment.

The new criteria and guidelines incorporate two notable changes:

- (1) They identify three stages of Alzheimer's disease, with the first occurring before symptoms such as memory loss develop. In contrast, for Alzheimer's disease to be diagnosed using the 1984 criteria, memory loss and a decline in thinking abilities must have already occurred.
- (2) They incorporate biomarker tests.

A biomarker is a biological factor that can be measured to indicate the presence or absence of disease, or the risk of developing a disease. For example, blood glucose level is a biomarker of diabetes, and cholesterol level is a biomarker of heart disease risk. Levels of certain proteins in fluid (for example, levels of beta-amyloid and tau protein in the cerebrospinal fluid and blood) are among

several factors being studied as possible biomarkers for Alzheimer's.

Biomarker Testing to Confirm Diagnosis

The 2011 criteria and guidelines identify two biomarker categories:

- Biomarkers showing the level of beta-amyloid accumulation in the brain
- Biomarkers showing that neurons in the brain are injured or actually degenerating

Many researchers believe that future treatments to slow or stop the progression of Alzheimer's disease and preserve brain function (called "disease-modifying" treatments) will be most effective when administered during the preclinical and MCI stages of the disease (Alzheimer's Association, 2014).

Biomarker tests will be essential to identify which individuals are in these early stages and should receive disease-modifying treatment. They also will be critical for monitoring the effects of treatment. At this time, however, more research is needed to validate the accuracy of biomarkers and better understand which biomarker test or combination of tests is most effective in diagnosing Alzheimer's disease (Alzheimer's Association, 2014).

The most effective test or combination of tests may differ depending on the stage of the disease and the type of dementia (Bloudek et al., 2011 in Alzheimer's Association, 2014).

Biomarker Testing to Confirm Diagnosis

Did you know?

Researchers hope one day to develop an easy-to-administer, reliable and inexpensive biomarker—a test that indicates harmful changes taking place in the brain—that can be used in a doctor's office. For example, eventually there may be a simple blood test to help diagnose Alzheimer's disease (Bernard, 2011).

Stages of Alzheimer's Disease - Stage 1

The National Institute on Aging / Alzheimer's Association Diagnostic Guidelines for Alzheimer's Disease cover three distinct stages of Alzheimer's disease:

Stage 1

Preclinical:

The preclinical stage, for which the guidelines only apply in a research setting, describes a phase in which brain changes, including amyloid buildup and other early nerve cell changes, may already be in process. At this point, significant clinical symptoms are not yet evident. In some people, amyloid buildup can be detected with positron emission tomography (PET) scans and cerebrospinal fluid (CSF) analysis, but it is unknown what the risk for progression to Alzheimer's dementia is for these individuals. However, use of these imaging and biomarker tests at this stage are recommended only for research. These biomarkers are still being developed and standardized and are not ready for use by clinicians in general practice.

Stages of Alzheimer's Disease

Did you know?

Although the 2011 criteria and guidelines identify preclinical disease as a stage of Alzheimer's, they do not establish diagnostic criteria that doctors can use now. Rather, they state that additional research is needed before this stage of Alzheimer's can be identified.

Test Yourself

In the Pre-Clinical Phase of Alzheimer's disease, individuals have measurable changes in the brain, cerebrospinal fluid and/or blood (biomarkers) that indicate the earliest signs of disease, but they have not yet developed noticeable symptoms such as memory loss.

- A. True
- B. False

The correct answer is: A. True.

The preclinical stage describes a phase in which brain changes may already be in process, but significant clinical symptoms are not yet evident.

Mild Cognitive Impairment (MCI) - Stage 2

Stage 2

Mild Cognitive Impairment (MCI):

The guidelines for the MCI stage are also largely for research, although they clarify existing guidelines for MCI for use in a clinical setting. The MCI stage is marked by symptoms of memory problems, enough to be noticed and measured, but not compromising a person's independence.

People with MCI may or may not progress to Alzheimer's dementia.

Researchers will particularly focus on standardizing biomarkers for amyloid and for other possible signs of injury to the brain. Currently, biomarkers include elevated levels of tau or decreased levels of beta-amyloid in the CSF, reduced glucose uptake in the brain as determined by PET, and atrophy of certain areas of the brain as seen with structural magnetic resonance imaging (MRI). These tests will be used primarily by researchers, but may be applied in specialized clinical settings to supplement standard clinical tests to help determine possible causes of MCI symptoms (NIA, 2014).

Alzheimer's Dementia - Stage 3

Stage 3

Alzheimer's Dementia:

These criteria apply to the final stage of the disease, and are most relevant for clinicians and patients. They outline ways clinicians should approach evaluating causes and progression of cognitive decline.

The guidelines also expand the concept of Alzheimer's dementia beyond memory loss as its most central characteristic. A decline in other aspects of cognition, such as word-finding, vision/spatial issues, and impaired reasoning or judgment may be the first symptom to be noticed.

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At this stage, biomarker test results may be used in some cases to increase or decrease the level of certainty about a diagnosis of Alzheimer's dementia and to distinguish Alzheimer's dementia from other dementias.

Symptoms

Symptoms are divided into two categories: **cognitive** (intellectual) and **psychiatric**.

Differentiating between cognitive and psychiatric symptoms is important so that behavioral problems that are caused by loss of cognitive functioning are not treated with anti-psychotic or anti-anxiety medications.

Cognitive Symptoms

Cognitive symptoms are ***amnesia, aphasia, apraxia and agnosia*** (the 4 As of Alzheimer's):

Amnesia is defined as loss of memory, or the inability to remember facts or events. We have two types of memories: the short-term (recent, new) and long-term (remote, old) memories. Short-term memory is programmed in the temporal lobe, while long-term memory is stored throughout extensive nerve cell networks in the temporal and parietal lobes. In AD, short-term memory storage is damaged first.

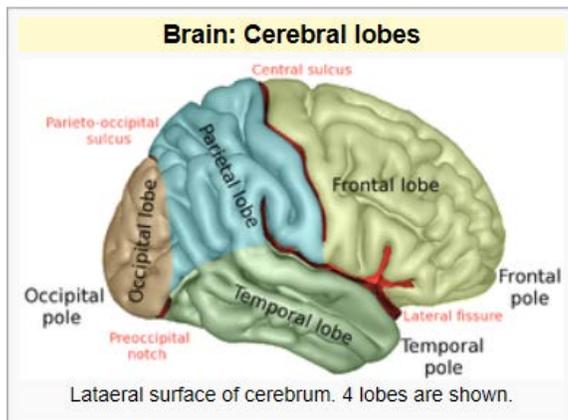


Image courtesy of Sebastian023 (2012), provided under the Creative Commons Attribution-Share Alike 3.0 License. (http://en.wikipedia.org/wiki/Lobes_of_the_brain)

Cognitive Symptoms

Aphasia is the inability to communicate effectively. The loss of ability to speak and write is called expressive aphasia. An individual may forget words he has learned, and will have increasing difficulty with communication. With receptive aphasia, an individual may be unable to understand spoken or written words or may read and not understand a word of what is read. Sometimes an individual pretends to understand and even nods in agreement; this is to cover-up aphasia. Although individuals may not understand words and grammar, they may still understand non-verbal behavior, i.e., smiling.

Apraxia is the inability to do pre-programmed motor tasks, or to perform activities of daily living such as brushing teeth and dressing. An individual may forget all motor skills learned during development. Sophisticated motor skills that require extensive learning, such as job-related skills, are the first

functions that become impaired. More instinctive functions like chewing, swallowing and walking are lost in the last stages of the disease.

Agnosia is an individual's inability to correctly interpret signals from their five senses. Individuals with Alzheimer's disease may not recognize familiar people and objects. A common yet often unrecognized agnosia is the inability to appropriately perceive visceral, or internal, information such as a full bladder or chest pain.

Psychiatric Symptoms

Major psychiatric symptoms include personality changes, depression, hallucinations and delusions.

Personality changes can become evident in the early stages of Alzheimer's disease. Signs include irritability, apathy, withdrawal and isolation. Individuals may show symptoms of depression at any stage of the disease. Depression is treatable, even in the latter stages of Alzheimer's disease.

Psychotic symptoms include hallucinations and delusions, which usually occur in the middle stage. Hallucinations typically are auditory and/or visual, and sensory impairments, such as hearing loss or poor eyesight, tend to increase hallucinations in the elderly. Hallucinations and delusions can be very upsetting to the person with the disease. Common reactions are feelings of fear, anxiety and paranoia, as well as agitation, aggression and verbal outbursts.

Individuals with psychiatric symptoms tend to exhibit more behavioral problems than those without these symptoms (NIA, 2014). It is important to recognize these symptoms so that appropriate medications can be prescribed and safety precautions can be taken.

Psychotic symptoms can often be reduced through the carefully supervised use of medications.

Variability in Presentation of Symptoms

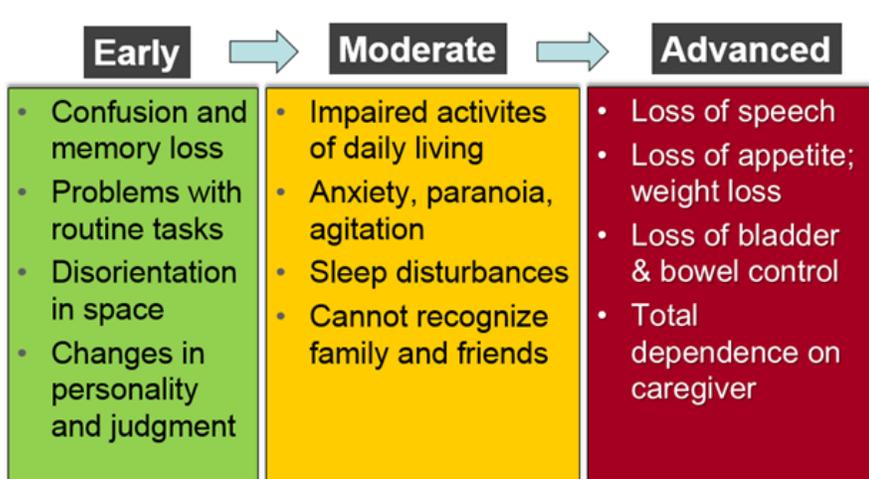
Although Alzheimer's disease affects people in different ways, the most common initial symptom is a gradually worsening ability to remember new information (Alzheimer's Association, 2014). This occurs because the first neurons to malfunction and die are usually neurons in brain regions involved in forming new memories. As neurons in other parts of the brain malfunction and die, individuals experience other difficulties.

The following are common symptoms of Alzheimer's:

- Memory loss that disrupts daily life.
- Challenges in planning or solving problems.
- Difficulty completing familiar tasks at home, at work or at leisure.
- Confusion with time or place.
- Trouble understanding visual images and spatial relationships.
- New problems with words in speaking or writing.

- Misplacing things and losing the ability to retrace steps.
- Decreased or poor judgment.
- Withdrawal from work or social activities.
- Changes in mood and personality, including apathy and depression.

Summary of Signs and Symptoms at Different Stages of AD



(Agins, 2014)

Progression of the Disease

Individuals progress through Alzheimer's at different rates. As they pass through different stages of the disease, individuals' cognitive and functional abilities decline. In the final, advanced stage of the disease, people need help with basic activities of daily living, such as bathing, dressing, eating and using the bathroom; lose their ability to communicate; fail to recognize loved ones; and become bed-bound and reliant on around-the-clock care. When individuals have difficulty moving, they are more vulnerable to infections, including pneumonia.

Alzheimer's-related pneumonia is often a contributing factor to the death of people with Alzheimer's disease (Alzheimer's Association, 2014).

Treatment

Currently, there is no cure for Alzheimer's disease but there are some pharmacological and non-pharmacological therapies that may help control some symptoms and slow down the progression of the disease.

The overall goal of pharmacologic treatment should be reduction, not eradication, of the most troublesome behaviors (Agins, 2014).

Cholinesterase Inhibitors

Acetylcholine is a neurotransmitter that helps with memory and thinking. In AD, acetylcholine is broken down and less acetylcholine is produced over time. Cholinesterase inhibitors help limit the

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amount of acetylcholine breakdown, but they cannot stop or reverse the destruction of brain cells and loss of acetylcholine that occur in AD.

Cholinesterase inhibitors do not prevent the disease from getting worse, but they may slow down the progression of the disease.

Cholinesterase inhibitors include:

- **RazadyneE® (galantamine):** Is approved for mild to moderate AD.
- **Exelon® (rivastigmine):** Is approved in pill and patch form for mild to moderate AD, and in a higher dosage Exelon Patch for severe AD.
- **Aricept® (donepezil):** Aricept 5mg and 10 mg are indicated for mild to moderate Alzheimer's disease, and Aricept 10 mg and 23 mg are indicated for moderate to severe Alzheimer's disease.

Cholinesterase Inhibitors

These drugs may help delay or prevent symptoms from becoming worse for a limited time and may help control some of the behavioral symptoms.

As the disease progresses, the brain produces less and less acetylcholine; therefore, cholinesterase inhibitors may eventually lose their effect. There are no published study results to compare these medications but because these medications work in a similar way, it is not expected that switching from one of these drugs to another will produce significantly different results (Agins, 2014). For unknown reasons, an Alzheimer patient may respond better to one drug than another.

Pharmacologic treatments should be governed by a “start low, go slow BUT go somewhere” philosophy and a mono-sequential approach is recommended (Agins, 2014).

Cholinesterase Inhibitors

Did you know?

Researchers are continually testing the effectiveness of various drug therapies that will control symptoms; slow, reduce and/or reverse mental and behavioral symptoms; and prevent or halt the disease. The historic "National Plan to Address Alzheimer's Disease," released by the U.S. Department of Health and Human Services in May 2012 and updated annually, calls for preventing and effectively treating Alzheimer's disease by 2025.

Summary of Cholinesterase Inhibitors

MOA	Cholinesterase Inhibitors		
Drug	Donepezil	Galantamine	Rivastigmine
Indication	Mild-moderate AD; severe AD	Mild-moderate AD	Mild-moderate AD

Initial dose	Tablet: 5 mg qd	Tablet/oral solution: 4 mg bid ER capsule: 8 mg qd	Capsule/oral solution: 1.5 mg bid Patch: 4.6 mg qd
Maximal dose	Tablet: 10 mg qd 23 mg qd	Tablet/oral solution: 12 mg bid ER capsule: 24 mg qd	Capsule/oral solution: 6 mg bid Patch: 9.5 mg qd

(Agins, 2014)

Treatment for Moderate to Severe AD: NMDA

Moderate to severe AD is best managed with Namenda® (memantine), which is an N-methyl D-aspartate (NMDA) antagonist. Memantine hydrochloride (twice-daily oral NAMENDA and once-daily NAMENDA XR capsules) for the treatment of moderate to severe Alzheimer's disease is currently recommended, but the sale of NAMENDA twice-daily tablets is being discontinued effective August 15, 2014 (Agins, 2014).

Studies have shown that the main effect of Namenda® is to delay progression of some of the symptoms of moderate to severe AD. The medication may allow patients to maintain certain daily functions a little longer. For example, Namenda® may help a patient in the later stages of AD maintain his or her ability to go to the bathroom independently for several more months, a benefit for both patients and care givers (Agins, 2014).

Namenda® is believed to work by regulating glutamate, another important brain chemical that, when produced in excessive amounts, may lead to brain cell death. Because NMDA antagonists work very differently from cholinesterase inhibitors, the two types of drugs can be prescribed in combination. The recommended effective dosage of Namenda® is 20 mg/day after the patient has successfully tolerated lower doses (Agins, 2014).

Dosage and Side Effects

Side effects of cholinesterase inhibitors may include nausea, vomiting, diarrhea and indigestion. Serious side effects requiring immediate attention may include swelling of the lips, tongue or throat or trouble breathing.

Patients are usually started on low drug doses and the dosage is gradually increased, based on effect and how well a patient tolerates the drug.

There is some evidence that certain patients may benefit from higher doses of the cholinesterase inhibitor medications. However, the higher the dose, the more likely the possibility of side effects. Adverse effects of cholinesterase inhibitors are related to the enhancement of cholinergic activity. Advising the patient to take the medication with food may minimize these effects.

Patients may be drug sensitive in other ways, and they should be monitored when a drug is started. Patients and care givers should report any unusual symptoms to the prescribing physician right away.

Some of these medications can be used alone or in combination, and may help slow progression of symptoms and improve quality of life (Agins, 2014).

Psychotropics for Behavior Issues

In patients with moderate to severe AD, specific behavioral problems can be most effectively managed by the addition of psychotropic agents, such as antipsychotics and antidepressants.

However, the use of any psychotropic agent in AD is somewhat controversial, and there is minimal evidence supporting the efficacy of any psychotropic drug in controlled trials (Agins, 2014).

It is also important to note that an increased risk of mortality has been observed in elderly patients with dementia treated with antipsychotic agents in controlled trials, mainly due to cardiovascular events and infections. Black Box warnings are now required by the FDA for antipsychotic agents (Alzheimer's Association, 2014).

Currently, research supports behavioral management interventions for individuals with dementia, as well as education, counseling and other support services for caregivers.

Psychotropics for Behavior Issues

Did you know?

Behaviors for which drugs will not help include:

- Wandering
- Pacing
- Hoarding or rummaging

(Agins, 2014).

Non-Pharmacological Interventions

A wide range of non-pharmacologic interventions have been proposed, but few have sufficient documented evidence to supporting their effectiveness (Alzheimer's Association, 2014).

Of the 25 categories of non-pharmacologic therapies reviewed in the Cochrane Database, only cognitive stimulation had findings that suggested a beneficial effect (Alzheimer's Association, 2014). Cognitive training, **cognitive stimulation** and training in activities of daily living appeared most successful in reaching the aims of the interventions (Olazaran et al., 2010 in Alzheimer's Association, 2014). Examples of cognitive stimulation include activities such as word games, number games, and word association exercises.

Research has shown that the most successful non-pharmacological interventions for neuropsychiatric symptoms of dementia are multicomponent, tailored to the needs of the caregiver and person with dementia, and delivered at home with periodic follow-up (Brodaty & Arasaratnam, 2012 in Alzheimer's Association, 2014).

Prevention Measures

Although there is no solid or unequivocal evidence that any of the following preventative measures can truly lower risk for Alzheimer's, it is still recommended that caregivers encourage the following behaviors in patients at risk for AD:

- Physical exercise
- Mental stimulation
- Specific diets
- Specific vitamins or dietary supplements
- Stress reduction
- Consumption of caffeine (Arendash, 2010)

Education and Care

Caregiving Tips: Daily Routines

Daily routines are sacred for most people. When caring for individuals with dementia, sticking to a routine is not only sacred, but a necessity.

Since change is difficult for individuals with AD, a structured schedule can meet two objectives: relieving caregiver stress and helping individuals maintain their abilities.

Consider this:

- Involve the individual in daily tasks. Disrupting his usual habits may result in an inability to perform that activity. For example, if you begin dressing him, he might soon forget how to dress himself. Participation also helps to maintain the person's self-esteem.
- Be realistic about what the individual can do given his degree of impairment. This will result in less frustration on both your parts.
- Bathing should follow the individual's routine prior to onset of the disease unless specific hygiene needs arise. If they previously showered in the evening, they should continue that pattern. However, keep in mind that changes may be necessary due to the progression of the disease. For example, someone who normally bathes at night might have to switch to the morning if they wake up soiled or if they are experiencing "sundowning" (behavioral problems toward evening).
- Repeating the same act may be meaningful for the individual and provide relief of tension. For example, an individual spends 20 minutes tearing a tissue or wiping the kitchen counter. If the activity does not seem to disturb the person, he or she should be allowed to continue. If the activity is of concern to the patient or caregiver, the activity should be gently redirected.
- Be consistent. If you say that you are going to do something, follow through with it.

Communication: Techniques

"It's not what you say, but how you say it." This expression holds doubly true when communicating with individuals with dementia (Alzheimer's Association, 2014).

Alzheimer's disease or related illnesses impair a person's ability to understand words and to speak. However, they can still benefit from non-verbal communication — body language, voice tone and

facial expressions. As the individual's ability to process verbal information declines, the importance of how caregivers communicate with them, verbally and non-verbally, increases.

Tips

Here are some tips from the Alzheimer's Foundation (2014) to enhance interactions:

- Remember that the individual with dementia might be feeling confused, anxious, irritable and depressed, and suffering from low self-esteem.
- Speak clearly, slowly, and in a calm and friendly tone.
- Be aware of body language. Individuals with dementia are very receptive to body language. They are often able to detect if a person's body language depicts happiness, anger or other emotions, and then mimic the cues they see. If a frustrated caregiver, for example, gives off a certain negative energy, the individual with the disease might mirror back the emotion and respond with an equal amount of anger or impatience.
- Use visual cues, pointing to things to show what you mean. Instead of saying, "Please brush your teeth," pick up the toothbrush and demonstrate, for instance.
- Make certain that the person with dementia has the best chance of seeing and hearing you. This involves checking that the person is wearing glasses and hearing aids, if necessary, and that talking occurs in a quiet environment.
- Approach the individual from the front. An unexpected touch or drawing near from behind may startle and upset the person.
- Before asking the individual to do something, address the person by name to get his attention. While you are speaking, maintain eye contact to help him focus.
- Ask only one question at a time and allow time for an answer. If he does not seem to understand, repeat the question using the same wording. If this does not work, after a few minutes, rephrase it.
- Allow the individual adequate time to respond in conversation or when performing an activity. Rushing will increase confusion.
- If the individual repeatedly asks a question, keep in mind that he cannot remember the response you have just given him. Instead of answering the question after a second or third repetition, reassure the individual in some way-everything is fine, you will be with him, you will help him.
- Eliminate distractions, such as the TV or radio, when talking to the person with dementia.
- Avoid statements that sound negative. For example, instead of "Don't go outside," say, "Stay inside."
- Use humor whenever possible, though not at the individual's expense.
- Break down all tasks into simple steps. Tell the individual one step at a time what to do. Giving too many directions at once or too quickly will increase confusion. If the individual gets upset and becomes uncooperative, stop and try again later.
- Keep on talking, even when a person may no longer be verbal. Chat about things that mattered to the person and mention names of family and friends. Even if communication is one-sided, it can loudly show that you care.
- Assess the situation. Once you have observed the person's behavior, try to find out what might have caused it. Ask yourself questions such as "Why is my loved one upset?" or "What happened

in the last few minutes that could have prompted this behavior?” Also, do a basic evaluation to cover all your bases: consider that the person could be cold, hungry, in pain, bored, threatened, sleepy, frightened, etc. Once you assess the root cause of this behavior, you can communicate accordingly.

- Offer comfort. Caregivers can provide comfort or reassurance through validation—a technique that allows the person to stay in the moment without being proven wrong or brought back to reality. For instance, if an older man becomes upset because he cannot find his mother, an effective response might be: “I know you miss your mother very much, and she loves you too. You were always your mother’s pride and joy.” This will help the individual feel understood and safe.
- Distraction is a powerful tool that diverts a person’s attention and can help minimize disruptive behaviors. Since individuals with dementia have a very small window of short-term memory, changing the subject will help the individual focus on something positive while leaving sadness or anger behind. Any distraction topic could work, as long as it is pleasant for the individual with the illness. This could range from the weather outside, to the painting on the wall, to the wedding story that the individual loves to tell over and over again.

Communication also plays a big role in behavior management.

Conclusion

AD is a chronic, challenging condition for the patient, family, and healthcare providers. Improving our knowledge about this condition, treatments and outcomes will assist all in managing this non-preventable disease.

Researchers have come a long way in their understanding of AD. Findings have clarified differences between normal age-related memory changes, mild cognitive impairment, and AD. Scientists also have made great progress in defining the changes that take place in the AD brain and have identified clinical biomarkers for earlier diagnosis. The integration of these biomarkers into clinical practice is a promising concept and will allow clinicians to more accurately pinpoint possible targets for treatment.

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