

Alzheimer's Disease

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Alzheimer's disease is the most common cause of dementia. It is characterized by specific microscopic changes in the brain and by a fairly distinct profile of cognitive (mental) decline. The primary microscopic changes are neuritic plaques and neurofibrillary tangles (Figure 1), which accumulate over time in discrete brain areas. For most people with Alzheimer's disease, an early prominent symptom is poor memory for recent events. Impairments in other cognitive abilities become more apparent later in the disease course.

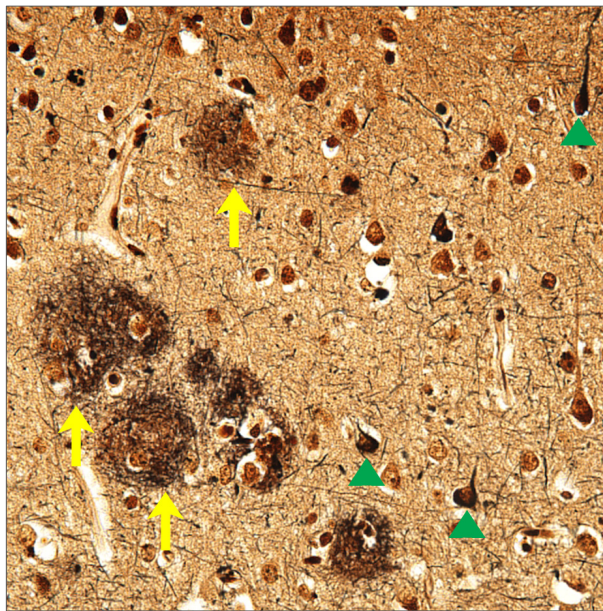


Figure 1. Microscopic changes of Alzheimer's disease. Neurofibrillary tangles are shown inside nerve cell bodies (green triangles) and neuritic plaques (yellow arrows) are in spaces between cell bodies. Bielschowsky silver stain. Image courtesy of Dr. Edward D. Plowey, Stanford University.

Dementia

Alzheimer's disease is one of several causes of dementia. Dementia is characterized by two key features. The first is cognitive (mental) decline. The second is an adverse impact on function or independence.

Cognitive decline might be reported by the patient himself or herself, reported by a family member, or inferred from results of mental testing by a physician or psychologist. Decline can be assessed more directly based on repeated mental status testing over time.

A work group sponsored by the National Institute on Aging and the Alzheimer's Association set the threshold for dementia as cognitive decline that interferes with function at work or with usual activities. In the Diagnostic and Statistical Manual, the American Psychiatric Association set the threshold as cognitive decline that interfere with independence in everyday activities, such as paying the bills.

The term mild cognitive impairment (MCI) is used to describe cognitive decline beyond what can be explained by age alone, but does not impair function or affects function only minimally. Some people with MCI will progress over time to dementia.

Clinical criteria for Alzheimer's disease

The National Institute on Aging and Alzheimer's Association work group has offered a definition for "probable Alzheimer's disease dementia." The work group used the word "probable" to indicate that a definite diagnosis usually requires documentation of plaques and tangles during a brain autopsy. The definition describes memory loss as the most common presentation (Table 1). The definition also acknowledges unusual forms of Alzheimer's disease that spare memory skills early on. One form includes prominent deficits in speech and speech understanding. In other forms, there may be prominent deficits in spatial abilities or executive functions (for example, skills required for planning, reasoning, and judgment).

Table 1. Alzheimer's disease clinical criteria

- A. Dementia, established by clinical examination
- B. Deficits in at least two cognitive domains
- C. Insidious symptom onset, with a clear history of cognitive decline
- D. Initial and most prominent cognitive deficits within one of four categories:
 - Amnesic (memory) presentation (most common)
 - Aphasic (speech and language) presentation
 - Visual-spatial disturbance presentation
 - Executive dysfunction presentation (problems with reasoning, judgment, and problem solving)
- E. No evidence a neurological or medical disorder that could have a substantial effect on cognition (e.g., stroke or another cause of dementia)

(after McKhann et al., 2011)

Clinical presentation

The plaque and tangle changes of Alzheimer's disease develop over a period of years before clinical symptoms ever appear. Cognitive decline begins gradually, often noticed only in retrospect, and gradually worsens until there is dementia.

Poor memory is usually the first change noticed by family members. The person with early symptoms may forget recent conversations and appointments. Often, he or she repeats questions and familiar stories. This form of memory especially depends on the hippocampus and nearby regions of the temporal lobes of the brain. This brain area shows microscopic changes of Alzheimer's disease very early in the course of the disease. Remote memories, such as events that happened in childhood and earlier adult life, involve other areas of the cerebral cortex. Remote memories are spared early in the illness.

Symptoms of Alzheimer's disease worsen gradually. Dementia due to strokes can decline in a stepwise manner, with sudden worsening followed by periods of stable cognition. Over time, mental abilities other than memory are affected. There may be problems with concentration and attention, multi-tasking, judgment and reasoning, speech and understanding, perceptual skills, and skilled movements. Behavior or mood are sometimes affected. Many people with even mild dementia appear less motivated and generally disinterested. Sometimes there is also depression, irritability, or delusions. Prominent behavioral changes that occur early in the disease course are more typical of a different type of dementia (frontotemporal dementia).

The threshold for dementia is crossed once mental decline has impaired function and independence. There may be problems using a mobile phone or computer, driving an automobile, keeping track of bills, operating a microwave oven, or preparing meals. Judgment is impaired, and some patients fall victim to financial scams. Over a period of several years or longer, the person with dementia becomes unable to perform basic daily activities and needs assistance with dressing, bathing, or brushing teeth. Some may fail to recognize family members or even their own reflection in a mirror. Movement and coordination are often spared until late into the course of the illness, and some people become bedridden. Life expectancy is reduced, often by pneumonia or by some other infection.

Evaluation and diagnosis

In most instances, a diagnosis of Alzheimer's disease should be made or confirmed by a geriatrician, neurologist, or geriatric psychiatrist. A neurologist is best qualified to recognize and diagnose another neurological condition causing dementia and mimicking Alzheimer's disease.

The physician's evaluation is directed towards documentation of dementia and determining its cause. The assessment includes a careful medical, neurological, and psychiatric history; a family history to see whether close family members have a similar or related disorder; a general physical examination; and a neurological examination. The physician reviews the use of prescription and over-the-counter medications. Many older adults take multiple drugs, some of which can impair mental function.

The physician's evaluation includes a mental status examination of memory and other cognitive abilities, sometimes supplemented by more detailed testing by a neuropsychologist. The physician should specifically consider the possibility of underlying depression.

Laboratory tests depend on the individual circumstances but usually include a screening blood test for kidney, liver, and related metabolic functions; a blood test for thyroid function; a blood test to determine the level of vitamin B12; and brain imaging. Brain imaging with a CT (computed tomography) scan or MRI (magnetic resonance imaging) scan is used to evaluate brain structures and to help exclude stroke, tumor, and other less common causes of dementia. None of these tests can prove the presence of Alzheimer's disease.

Certain spinal fluid tests and certain PET (positron emission tomography) brain scans can measure biochemical changes associated with Alzheimer's disease. These tests are sometimes ordered to increase — or decrease — the likelihood of Alzheimer disease in unusual situations.

Treatment and management

There is not yet a cure for Alzheimer's disease. People with Alzheimer's disease can be helped by environmental adjustments and by prescription drugs.

Environmental adjustments

Environmental adjustments help compensate for declining mental abilities. A bulletin board or white board, or a written or electronic calendar can help some patients keep track of appointments and upcoming events.

Compartmentalized pill boxes can be used to organize medications. A person with dementia almost always requires help with more complex tasks like managing bills and finances, or simply maintaining a household. People with more severe dementia often need help with bathing, dressing, toileting, and eating.

Driving skills can deteriorate and people with dementia, even mild dementia, face a higher than average risk of accidents. In California, physicians are required by law to report a diagnosis of Alzheimer's disease. The loss of a driver's license is not automatic, however, and some people with mild dementia can retain their licenses.

Although the evidence for benefit is circumstantial, most physicians recommend regular physical exercise, mental stimulation, social engagement, and good nutrition. Brisk walking and other forms of aerobic exercise are usually recommended when there are no health problems standing in the way. One target goal is to walk about 150 minutes each week, divided into 30 minute intervals, five days each week.

Mental activity is potentially important. People obtain mental stimulation through social interactions, hobbies, card games and board games, and reading. There is no evidence that one form of mental stimulation — such as a set of computerized tasks — is better than another.

Drugs

Two classes of prescription medications have been approved for treatment of dementia caused by Alzheimer's disease (Table 2). These medications sometimes improve symptoms modestly, but they are not able to halt or reverse the underlying disease.

The first class is cholinesterase inhibitor. Members of this class boost levels of acetylcholine in the brain. Acetylcholine is a neurotransmitter involved with alertness, concentration, and memory. Commonly prescribed cholinesterase inhibitors are donepezil, rivastigmine, and galantamine. There is no good evidence that one is more effective than another.

The second class of approved drugs blocks a nerve cell ion channel (the *N*-methyl-D-aspartate receptor [NMDA receptor]), where excessive activation could harm the nerve cell. Memantine is the only approved drug in this class, and it is approved only for moderate and severe dementia due to Alzheimer's disease. There is little evidence that it helps people with mild dementia or slows dementia progression.

Table 2. Drugs approved for dementia due to Alzheimer's disease

<i>Drug name</i>	<i>Usual effective dose</i>
Cholinesterase inhibitor	
Donepezil	5 or 10 mg by mouth once daily; or 23 mg extended release by mouth once daily
Rivastigmine	4.5 or 6 mg by mouth twice daily; or 9.5 mg or 13.3 mg by transdermal patch once daily
Galantamine	8 or 12 mg by mouth twice daily; or 16 or 24 mg extended release by mouth once daily
NMDA receptor blocker	
Memantine	10 mg by mouth twice daily; or 28 mg extended release by mouth once daily

Dosing information is for illustrative purposes and is not intended to guide treatment decisions. Treatment often begins at lower dosages. For some drugs, other dosages and other formulations are available. There are potential side effects and risks to these drugs. (after Henderson & Kerchner, 2014)

Other drugs can be used if there are problems with mood or disruptive behaviors. An antidepressant may help depression even though it may have little or no effect on cognitive impairment.

A few people with dementia become agitated or aggressive. These symptoms are sometimes caused by a medical illness like a bladder infection, by a medication side-effect, or by a change in the patient's daily routine. It is important to search carefully for these underlying conditions. When no specific cause can be found and when agitation or aggression poses a safety risk, the physician may try other prescription medications for these symptoms. The concern, of course, is that other medications have potential side effects, as well. Some drugs used for agitation can increase confusion and can increase risk of falling.

Patients and their families are tempted to try dietary supplements and herbal remedies. This approach is understandable, since approved prescription medicines are only modestly effective. However, very few alternative therapies have ever been subjected to rigorous testing in humans, and there is no evidence that they are at all effective. Alternative therapies can be expensive. Like prescription drugs, they can cause side effects, and they might interact adversely with prescription drugs. Most physicians advise against these products.

References

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McKhann, G.M., Knopman, D.S., Chertkow, H., et al. (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. *Alzheimers Dement.* 7, 263-269.

Resources

Alzheimer's Association
www.alz.org

National Institute on Aging, Alzheimer's Disease Centers
<https://www.nia.nih.gov/research/dn/alzheimers-disease-centers>

National Institute on Aging, Alzheimer's disease information resources
www.niahttps://www.nia.nih.gov/health/alzheimers

National Institute on Aging, Alzheimer's disease fact sheet
www.nia.nih.gov/alzheimers/publication/alzheimers-disease-fact-sheet

Stanford Alzheimer's Disease Research Center
adrc.stanford.edu

Stanford Center for Memory Disorders
<https://stanfordhealthcare.org/medical-clinics/memory-disorders-center.html>

Stanford Health Care Aging Adult Services
<https://stanfordhealthcare.org/medical-clinics/aging-adult-services.html>

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