34 Update on Dementia. Pathophysiology, Diagnosis, and Treatment. DSM-IV versus DSM-V

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Abstract

Dementia is frequent in the elderly, and advancing age is the strongest risk factor. It includes Alzheimer's disease (AD), Vascular dementia (VaD), and other neurogenerative disorders such as Lewy body dementia (LBD), and other less-common neurodegenerative dementing diseases, such as frontotemporal dementia (FTD). All this acquired disorder of cognition and the related behavioral impairment interferes with social and occupational functioning. The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) present differences in the description of AD and VaD. The new DSM recognizes the acceptable alternative "neurocognitive disorder" as a newly preferred and more scientific term than "dementia". This new diagnosis includes both the dementia and amnesic disorder diagnoses from DSM-IV. Furthermore, DSM-V recognizes specific etiologic subtypes of neurocognitive dysfunction, such as Alzheimer's disease, Parkinson's disease, HIV infection, Lewy body disease, and Vascular disease. This is a review based on scientific evidence and information concerning the most common dementia, Alzheimer's disease (AD) and the second most important, Vascular dementia (VaD), and the main differences between the classifications of DSM-IV and DSM-V for both diseases.

Keywords

Dementia • Alzheimer's disease • Vascular dementia • Major and mild neurocognitive disorder • DSM–IV • DSM-V

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Introduction

According to many specific references such as the World Alzheimer Report 2015, the number of people living with dementia globally is expected

P.Á. Gargiulo, H.L. Mesones-Arroyo (eds.), *Psychiatry and Neuroscience Update - Vol. II*,
DOI 10.1007/978-3-319-53126-7_34

to rise from the current 46 million to 131.5 million by 2050. Global costs to treat dementia, estimated at about US$818 billion in 2015, are expected to soar to $1 trillion by 2018 and to $2 trillion by 2030 [1]. Dementia is most common in the elderly. Multiple neuropathologic processes may underlie dementia, including both neurodegenerative diseases and vascular disease. In addition, comorbidity (the presence of more than one disease process) is more common than dementia in elderly persons [2–5].

There are two most important dementias. Alzheimer's disease (AD) is the most common neurodegenerative disease responsible for dementia. About half of dementia cases result from AD [2, 3]. Many measurable AD pathologic changes occur in most cognitively intact elderly individuals who undergo autopsy. This indicates that AD is a chronic disease with latent and prodromal stages. It suggests that individuals may have varying abilities to compensate, either biologically or functionally, for the presence of pathological changes underlying AD [6].

Vascular dementia is the second most common form of dementia after AD. The condition is not a single disease. It is a group of syndromes related to different vascular mechanisms. Vascular dementia is preventable, but in this dementia early detection and an accurate diagnosis are also important [7].

It is clinically important to use the Hachinski Ischemic Score (HIS) which aims to distinguish Vascular dementia from Alzheimer's disease [8]. Hachinski's ischemic scale seems to be reliable approximately in 90% of cases in the differential diagnosis between Vascular and Alzheimer dementias, especially in the multi-infarct group [9]. The presence of 13 clinical symptoms comprises the HIS. It assigns two points to each of the following symptoms: abrupt onset, fluctuating course, history of stroke, focal neurologic signs, and focal neurologic symptoms. It also assigns additional points for stepwise deterioration, nocturnal confusion, preservation of personality, depression, somatic complaints, emotional incontinence, hypertension, and associated atherosclerosis. A score of 7 or higher suggests Vascular dementia, and a score of 4 or less suggests AD.

As has been mentioned, dementia includes a group of neurodegenerative disorders characterized by progressive loss of cognitive function and a decrease in the ability to perform daily living activities [10].

There are two American mental disorder classifications that could be used at present for diagnosis criteria of mental disorders: the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and the fifth edition (DSM-5). We are at a transitional point, discontinuing the use of the DSM-IV and starting use of the new DSM- V. It is true that some doctors have a strong resistance to the use of the DSM-V in respect of the new mental disorders classification. When the DSM-V was published, it led to many controversial medical and psychiatric opinions.

DSM-IV was published in 1994 and DSM-5 was published in 2013. The DSM-V is now the standard classification of mental disorders used by mental health professionals in the United States. It is intended to be used in all clinical settings by clinicians of different theoretical orientations. It can be used by mental health and other health professionals, including psychiatrists and other physicians, psychologists, social workers, nurses, occupational and rehabilitation therapists, and counselors. It can also be used in research in clinical and community populations [11]. We see great differences in the diagnosis of AD and Vascular dementia between the two classifications, and it is the purpose of this chapter to clarify these differences.

Alzheimer's Disease

Let's start with the history background of AD.This dementia was first described in 1901 by a German psychiatrist named Alois Alzheimer. He observed a patient at the Frankfurt Asylum named Mrs. Auguste D. This 51-year-old woman suffered from a loss of short-term memory, among other behavioral symptoms that puzzled Dr. Alzheimer [12]. After 5 years, in April 1906, the patient died, and Dr. Alzheimer sent her brain and her medical records to Munich, where he was

working in the lab of Dr. Emil Kraepelin. By staining sections of her brain in the laboratory, he was able to identify amyloid plaques and neurofibrillary tangles [12]. The important seminar given by Dr. Alzheimer on November 3, 1906, was the first time that the pathology and the clinical symptoms of the disorder had been presented together. The nosological entity was termed presenile dementia. Alzheimer published his findings in 1907 [13].

In the past 20 years, an effort has been made to understand the neurogenetics and pathophysiology of AD. Four different genes are definitively associated with AD. Other genes that may have a probable role have been identified. The mechanisms by which altered amyloid and tau protein metabolism, inflammation, oxidative stress, and hormonal changes may produce neuronal degeneration in AD are being elucidated, and rational pharmacologic interventions based on these discoveries are being developed [14].

Etiology

The cause of AD is unknown. But there are many possible risk factors to be considered. Many investigators now believe that converging environmental and genetic risk factors trigger a pathophysiologic cascade that, acting over decades, leads to Alzheimer pathology and dementia [15]. A group of risk factors for Alzheimer-type dementia have been identified [16–19]:

(a) Advancing age
(b) Family history
(c) APOE 4 genotype[1]
(d) Obesity
(e) Insulin resistance
(f) Vascular factors
(g) Dyslipidemia
(h) Hypertension
(i) Traumatic brain injury
(j) Inflammatory markers
(k) Down syndrome

Based on evidence, there are some other possible risk factors, like depression. Other important risk factors to consider are the genetic risk factors, which are described below in detail. However, there are also some protective factors, such education and long-term use of nonsteroidal anti-inflammatory drugs [22–24].

With regard to genetic factors, it has been described that in some families an autosomal dominant AD has been observed. It accounts for less than 5% of cases, and is almost exclusively early-onset AD. These cases occur in at least three individuals in two or more generations, with two of the individuals being first-degree relatives [25]. If we follow familial clustering, it represents approximately 15–25% of late-onset AD cases, and most often involves late-onset AD. In familial clustering, at least two of the affected individuals are third-degree relatives or closer [25].

Mutations in the following genes unequivocally cause early-onset autosomal-dominant AD:

1. Amyloid precursor protein (APP*)* gene on chromosome 21
2. Presenilin-1 (PS1) gene on chromosome 14
3. Presenilin-2 (PS2) gene on chromosome 1

All three of these genes lead to a relative excess in the production of the stickier 42-amino acid form of the Ab peptide over the less sticky 40-amino-acid form [25].

It has been postulated that beta-pleated peptide has neurotoxic properties, and that it leads to a cascade of events. These events are not well understood, and result in neuronal death, synapse loss, and the formation of neurofibrillary tangles (NFTs) and senile plaques (SPs), between other lesions. However, mutations that have been found to date only make it possible to explain less than half of the cases of early-onset AD [26]. Familial Alzheimer's disease is caused by any one of a number of different single-gene mutations, such as mutations on chromosome 21, which cause the

[1]The *APOE* gene (located on chromosome 19) is the only gene identified related to early-onset and late-onset of AD. APOE ε4 is called a risk-factor gene because it increases a person's risk of developing the disease; however, inheriting an APOE ε4 allele does not necessarily mean that a person will develop AD [20, 21].

formation of abnormal amyloid precursor protein (APP). Afterwards, several mis-sense genetic mutations within the APP gene were identified in these familial AD kindreds. These mutations resulted in amino acid substitutions in APP that appear to alter the previously described proteolytic processing of APP, generating amyloidogenic forms of Ab [26]. Approximately 50–70% of early-onset autosomal-dominant AD cases appear to be associated with a locus (AD3) mapped by genetic linkage to the long arm of chromosome 14 (14q24.3). Numerous mis-sense mutations have been identified on a strong candidate gene called PS1 [26].

There is another important gene. The gene encoding the cholesterol-carrying apolipoprotein E (APOE*)* on chromosome 19 has been linked to increased risk for AD, principally late-onset but also some early-onset cases. This gene is inherited as an autosomal codominant trait with three alleles. The APOE E2 allele, the least prevalent of the three common APOE alleles, is associated with the lowest risk of developing AD, with a lower rate of annual hippocampal atrophy, higher cerebrospinal fluid Aβ and lower phosphor-tau, suggesting less AD pathology [27, 28].

APOE E4 gene "dose" is correlated with increased risk and earlier onset of AD [29]. Blood pressure is very important in those individuals who are genetically predisposed to AD. They are advised to closely control their blood pressure. Hypertension has been shown to interact with APOE E4 genotype to increase amyloid deposition in cognitively healthy middle-aged and older adults. Controlling hypertension may significantly decrease the risk of developing amyloid deposits, even in those with genetic risk [30, 31].

Although research supports the relationship between the APOE ε4 variant and the occurrence of late-onset AD, the full mechanism of action and the pathophysiology are not known [20, 21].

There are also other genome-wide association studies that have identified additional susceptibility loci. They are the following: clusterin (CLU*)* gene, phosphatidylinositol-binding clathrin assembly protein *(*PICALM*)* gene, complement receptor 1 (CR1*)* gene, ATP-binding cassette sub-family A member 7 gene *(*ABCA7), membrane-spanning gene cluster (MS4A6A/MS4A4E), ephrin receptor A1 *(* EPHA1*),* CD33*,* CD2AP [26].

It is important to note that many APOE E4 carriers do not develop AD, and many patients with AD do not have this allele. The presence of an APOE E4 allele does not secure the diagnosis of AD, but instead, the APOE E4 allele acts as a biologic risk factor for the disease, especially in those younger than 70 years [14].

Other risk factor to describe is depression. Depression has been identified as a risk factor for AD and other dementias. Recent Framingham data have helped to bolster the epidemiological association. The study showed a 50% increase in AD and dementia in those who were depressed at baseline. During a 17-year follow-up period, a total of 21.6% of participants who were depressed at baseline developed dementia, as compared with 16.6% of those who were not depressed [32].

Pathophysiology

In the pathophysiology of normal aging and in AD, the pathologic hallmarks of AD are the same that occur in the brains of cognitively intact persons. In AD, tau is changed chemically. If we describes what happen it begins to pair with other threads of tau, which become tangled together. When this happens, the microtubules disintegrate, collapsing the neuron transport system. The formation of these neurofibrillary tangles (NFTs) may result first in communication malfunctions between neurons and later in the death of the cells. This is called apoptosis. In addition to NFTs, the anatomic pathology of AD includes senile plaques (SPs), also known as beta-amyloid plaques. They may be observed at the microscopic level, and cerebrocortical atrophy at the macroscopic level. The hippocampus and medial temporal lobe are the initial sites of tangle deposition and structure atrophy. This can be seen on brain magnetic resonance imaging early in AD and helps supporting a clinical diagnosis [33].

SPs and NFTs were described by Alois Alzheimer in his original report on the disorder in 1907 [13]. They are now universally accepted as the pathological hallmark of the disease.

Although NFTs and SPs are characteristic of AD, they are not pathognomonic. NFTs are found in several other neurodegenerative disorders. SPs may occur in normal aging. The only presence of these lesions is not sufficient to support the diagnosis of AD. It is important that symptoms and lesions must be present together in sufficient numbers and in a characteristic topographic distribution to fulfill the current histopathologic criteria for AD.

For example, in a study in which neuropathologists were blinded to clinical data, they identified 76% of brains of cognitively intact elderly patients as demonstrating AD [33]. The accumulation of SPs primarily precedes the clinical onset of AD. NFTs, loss of neurons, and loss of synapses accompany the progression of cognitive decline [34].

Diagnosis

Patients with Alzheimer's disease (AD) most commonly present insidiously progressive memory loss. Other spheres of cognitive impairment are added over several years. This loss may be associated with slowly progressive behavioral changes. After memory loss occurs, there are others symptoms that appear: language disorders (e.g., anomia) and impairment in their visuospatial skills and executive functions [14].

The diagnosis of Alzheimer's disease should include: signs and symptoms, with the diagnosis criteria as guidelines, biomarkers which confirm the diagnosis, blood test, imaging, neuoropsychological test and pathophysiology.

The symptoms of AD can be classified into the following stages:

(a) Preclinical
(b) Mild
(c) Moderate
(d) Severe

Preclinical Alzheimer's Disease

The pathologic changes begin in the entorhinal cortex, which is near the hippocampus and directly connected to it. AD then proceeds to the hippocampus, which is the structure that is essential to the formation of short-term and long-term memories. Affected regions begin to atrophy [14]. These brain changes probably start 10–20 years before any visible signs or symptoms appear. They could start in a silent way after 40 years of age. Memory loss, the first visible sign, is the main feature of amnestic mild cognitive impairment (MCI). Many scientists think MCI is often an initial, transitional clinical phase between normal brain aging and AD. A patient with preclinical AD may appear completely normal on physical examination and mental status testing. At this stage, there is normally no alteration in judgment or the ability to perform activities of daily living [14].

Mild Alzheimer's Disease

In the mild stage we can observe that the cerebral cortex is affected, memory loss continues and impairment of other cognitive abilities are also present. Later in the disease, physical abilities decline. The clinical diagnosis of AD is usually made during this stage. Signs and symptoms of mild AD can include the following:

Memory loss
Confusion about the location of familiar places (getting lost begins to occur)
Compromised judgment often leading to bad decisions
Taking longer to accomplish normal daily tasks
Trouble handling money and paying bills
Compromised judgment often leading to bad decisions
Loss of spontaneity and sense of initiative
Mood and personality changes
Increased anxiety

The growing number of plaques and tangles first damage areas of the brain that control memory, language, and reasoning. In mild AD, a person seems to be healthy but is actually having more and more trouble making sense of the world around him or her. The realization that something is wrong often comes gradually, because the early signs can be confused with changes that can

happen normally with aging. For example: in many cases, the family has a more difficult time handling the diagnosis than the patient does, some patients do not seem emotionally affected, probably because of the sense of apathy, a feeling which occurs in AD. In other cases, following the initial diagnosis, patients should be carefully monitored for a depressed mood. Although it is common for patients with early AD to be depressed about the diagnosis, they rarely become suicidal [14].

Moderate Alzheimer's Disease

After the mild stage, the moderate stage starts; damage continues to affect the cerebral cortex that controls language, reasoning, sensory processing, and conscious thought. Affected regions continue to atrophy, and signs and symptoms of the disease become more pronounced. Behavioral symptoms, such as wandering and agitation, can occur. More intensive supervision and care become necessary, and this can be difficult for many spouses and families.

The symptoms of this stage can include the following:

Increasing memory loss, confusion, and shortened attention span
Problems recognizing friends and family members
Repetitive statements or movement; occasional muscle twitches
Hallucinations, delusions, suspiciousness or paranoia, irritability
Difficulty with language; problems with reading, writing, working with numbers
Difficulty organizing thoughts and thinking logically
Inability to learn new things or to cope with new or unexpected situations
Restlessness, agitation, anxiety, tearfulness, wandering, especially in the late afternoon or at night
Loss of impulse control (shown through behavior, such as undressing at inappropriate times or places, or vulgar language)
Perceptual-motor problems (such as trouble getting out of a chair or setting the table)

Anger is a primary emotion that can mask underlying confusion and anxiety. Also, the risk of violent and homicidal behavior is highest at this stage of disease progression. Patients should be carefully monitored for any behavior that may compromise the safety of those around them. Since it is the case of a person who cannot remember the past or anticipate the future, the world around them can be strange and frightening. Staying close to a trusted and familiar caregiver may be the only thing that makes sense and provides security. The individual may constantly follow his or her caregiver and feel lost when the person is out of sight. Judgment and impulse control continue to decline at this stage [14].

Severe Alzheimer's Disease

In the last stage, illness severity is perceived. Plaques and tangles are widespread throughout the brain, and areas of the brain have been atrophied. Patients cannot recognize family and loved ones or communicate in any way. This is a burden for the families. They are completely dependent on others for care. All sense of self seems to disappear.

There are other symptoms:

Weight loss
Seizures, skin infections, difficulty swallowing
Groaning, moaning, or grunting
Increased sleeping
Lack of bladder and bowel control

In end-stage AD, patients may be in bed much or all of the time. Death is often the result of other illnesses, frequently aspiration pneumonia.

Clinical guidelines for the diagnosis of AD have been formulated by the National Institutes of Health–Alzheimer's Disease and Related Disorders Association (NIH-ADRDA); the American Psychiatric Association, in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)*;* and the Consortium to Establish a Registry in Alzheimer's disease (CERAD). In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association (AA) workgroup released new research and clinical diagnostic

criteria for AD [35]. The NIH–ADRDA criteria for the diagnosis of AD require the finding of a slowly progressive memory loss of insidious onset in a fully conscious patient. AD cannot be diagnosed in patients with clouded consciousness or delirium [35]. The focus of the 2011 NIA-AA criteria is the need to create a more accurate diagnosis of preclinical disease so that treatment can begin before neurons are significantly damaged, while they are more likely to respond. The report includes criteria for diagnosis of the following:

Asymptomatic, preclinical AD (for purposes of research, not clinical diagnosis) [36].
Mild cognitive impairment (MCI), an early symptomatic but predementia phase of AD [37]
AD dementia [38]

The diagnosis of AD also needs laboratory tests and biomarkers, imaging and neuropsychological tests. Alzheimer disease (AD) is a clinical diagnosis. But as we have mentioned, imaging studies and laboratory tests may be used. Used imaging studies are computed tomography [CT], magnetic resonance imaging [MRI] and, in selected cases, single-photon emission CT [SPECT] or positron-emission tomography [PET].

These tests help exclude other possible causes for dementia (e.g., cerebrovascular disease, cobalamin [vitamin B_{12}] deficiency, syphilis, thyroid disease [37]). Brain scanning with SPECT or PET is not recommended for the routine workup of patients with typical presentations of AD. These modalities may be useful in atypical cases, or when a form of frontotemporal dementia is a more likely diagnosis [39].

There are two important organizations working in early AD detection. They are the Amyloid Imaging Taskforce (AIT), an assembly of experts from the Alzheimer's Association, and the Society of Nuclear Medicine and Molecular Imaging (SNMMI). They developed guidelines for the use of amyloid β (Aβ) positron emission tomography (PET) imaging to clarify diagnoses of AD or frontotemporal dementia. It described that, amyloid imaging is appropriate in patients with persistent or progressive unexplained mild cognitive impairment, in those satisfying core clinical criteria for possible AD because of unclear clinical presentation, and in patients with progressive dementia and atypically early age of onset. The committee recommends against imaging in asymptomatic individuals and patients with a clear AD diagnosis with typical age of onset. Scanning cannot be used to stage dementia or determine its severity, and it should not be used in lieu of genotyping for suspected autosomal mutation carriers [40].

There are three imaging agents regularly used for diagnostic. The first one is the florbetapir F 18 (AMYViD). This was approved by the FDA in April 2012 as a diagnostic imaging agent. It is indicated for PET brain imaging of beta-amyloid neuritic plagues in adults. It has been evaluated in Alzheimer's disease but also in other cognitive declines [41–43].

The second was approved by the FDA in October 2013. It is the 18F–labeled Pittsburgh compound B (PIB) derivative, flutemetamol F18 injection (Vizamyl), for use with PET brain imaging in adults undergoing evaluation for Alzheimer disease and dementia. Like florbetapir F18, flutemetamol F18 attaches to beta-amyloid in the brain and produces a PET image that can be used to assess its presence. A positive scan indicates that there is likely a moderate or greater amount of amyloid in the brain, but it does not establish a diagnosis of Alzheimer's disease or other dementia. The effectiveness of flutemetamol F18 was established in two clinical studies with 384 participants who had a wide range of cognitive function [44].

The final and third agent, florbetaben F18 (Neuraceq), was approved by the FDA in March 2014. Images may be obtained between 45–130 min following the injected dose. FDA approval was based on safety data from 872 patients who participated in global clinical trials, as well as on three studies that examined images from adults with a range of cognitive function, including 205 end-of-life patients who had agreed to participate in a post-mortem brain donation program. Images were analyzed from 82 subjects with post-mortem confirmation of the presence or absence of beta-amyloid neuritic plaques [45]. Subjects in this study underwent testing of memory and executive function along

with fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scanning and amyloid deposition with C 11 Pittsburgh Compound B (PiB PET). The researchers found that amyloid burden and lower FDG metabolism (synaptic dysfunction) independently predicted episodic memory performance. Subjects with worse memory performance had higher PiB deposition and lower FDG metabolism in regions of the brain commonly affected in AD [46].

Cerebral spinal fluid (CSF) is a new biomarker. But routine measurement of cerebral spinal fluid tau and amyloid is not recommended except in research settings. Lumbar puncture for measurement of tau and amyloid may become part of the diagnostic workup when effective therapies that slow the rate of progression of AD have been developed, particularly if the therapies are specific for AD and carry significant morbidity [14]. It is observed in the CSF levels of tau and phosphorylated tau that are often elevated in AD, whereas amyloid levels are usually low. The reason for this is not known, but perhaps amyloid levels are low because the amyloid is deposited in the brain rather than the CSF. By measuring both proteins, sensitivity and specificity of at least 80–90% can be achieved [14].

Another research tool is the genotyping for apolipoprotein E (APOE) alleles. It has been helpful in determining the risk of AD in populations, but until recently it was of little, if any, value in making a clinical diagnosis and developing a management plan in individual patients. Numerous consensus statements have recommended against using APOE genotyping for predicting AD risk [25].

One of the neuropsychological tests used in the assessment of AD is the Mini-Mental State Examination (MMSE). It is often used to assess cognitive status. Health providers are increasingly using an alternative mental status test, the Montreal Cognitive Assessment (MoCA) to screen for cognitive impairment [47, 48].

There are many conditions for the differential diagnosis of Alzheimer's disease. One of them is depression. Depression is an important consideration in the differential diagnosis of Alzheimer's disease (AD). The clinical manifestations of depression overlap with those of AD. In addition, an estimated 30–50% of AD patients have comorbid depression [49]. The psychological tests for assessing depression (e.g., the Hamilton Scale for Depression, the Beck Depression Inventory, and the Geriatric Depression Scale) were designed for use in other patient populations, and may be less reliable in patients with AD. Consequently, the National Institute of Mental Health has developed provisional diagnostic criteria for depression in AD [49].

Treatment

The drugs approved by the US Food and Drug Administration (FDA) for AD treatment are few. All drugs approved by the FDA for the treatment of AD modulate neurotransmitters, either acetylcholine or glutamate, and these are only symptomatic therapies. The standard medical treatment for AD includes cholinesterase inhibitors (ChEIs) and a partial *N* -methyl-D-aspartate (NMDA) antagonist [50, 51].

Secondary symptoms of AD (e.g., depression, agitation, aggression, hallucinations, delusions, sleep disorders) can be problematic. Behavioral symptoms in particular are common, and can exacerbate cognitive and functional impairment. The following classes of psychotropic medications have been used to treat these secondary symptoms [52]: antidepressants, anxiolytics, antiparkinsonian agents, beta-blockers, antiepileptic drugs (for their effects on behavior), and neuroleptics or antipsychotics.

Most studies of psychotropic drugs for AD have demonstrated null or limited efficacy. Recent pharmacologic research in AD focuses principally on the development of disease-modifying drugs that can slow or reverse the progression of AD. Targets of these investigational agents have included beta-amyloid production, aggregation, and clearance, as well as tau phosphorylation and assembly. To date, none of these drugs has demonstrated efficacy in phase III trials [46].

There are many experimental therapies that have been proposed for AD. These include anti-amyloid therapy, reversal of excess tau phosphorylation, estrogen therapy, vitamin E therapy, and

free-radical scavenger therapy. Based on the evidence, the results are contradictory and disappointing. In the past 10 years, numerous antiamyloid therapy studies have been conducted to decrease toxic amyloid fragments in the brain, including studies of the following:

Vaccination with amyloid species
Administration of monoclonal antiamyloid antibodies
Brain shunting to improve removal of amyloid
Beta-secretase inhibitors to prevent generation of the A-beta amyloid fragment
Administration of intravenous immune globulin that may contain amyloid-binding antibodies
Selective amyloid-lowering agents
Chelating agents to prevent amyloid polymerization

Other therapeutic options such as direct current stimulation are being explored for a possible therapeutic role in AD. However, evidence of therapeutic benefit from these modalities is highly preliminary [53]. Disease-modifying therapies would delay the onset of AD and/or slow the rate of progression. Since brain changes associated with AD probably start decades before dementia becomes clinically apparent, many investigators believe that disease-modifying therapies are much more likely to be effective if they are started in a presymptomatic stage [53].

Neuropsychological, neuroimaging, and genetic methods are identifying patients at increased risk. Although phase III trials for several potential disease-modifying therapies have been completed, none of these agents have shown clear efficacy, and therefore have not yet been approved by the FDA [14]. Prevention could be a good choice. Evidence, largely epidemiologic, suggests that healthy lifestyles can reduce the risk of AD. Physical activity, exercise, cardiorespiratory fitness and Mediterranean diet may be protective [54, 55].

Vascular Dementia

Vascular dementia (VaD) is the second most common cause of dementia. It is observed in the United States and Europe, but it is the most common form in some parts of Asia and Latin America. This is a preventable dementia, but early detection and an accurate diagnosis are important. Patients who have had a stroke are at increased risk for VaD. Recently, vascular lesions also have been thought to play a role in AD [56].

The background history of VaD started early, in 1899. At first, arteriosclerosis and senile dementia were described as different syndromes. In 1969, Mayer-Gross et al. described this syndrome, and reported that hypertension is the cause in approximately 50% of patients. In 1974, Hachinski et al. coined the term multi-infarct dementia. In 1985, Loeb used the broader term vascular dementia. Recently, Bowler and Hachinski introduced a new term, vascular cognitive impairment [56].

If we describe the epidemiology of VaD, the prevalence rate is 1.5% in Western countries and approximately 2.2% in Japan. In Japan, Vascular dementia accounts for 50% of all dementias that occur in individuals older than 65 years. In Europe, Vascular dementia and mixed dementia account for approximately 20% and 40% of cases, respectively. In Latin America, 15% of all dementias are vascular. In community-based studies in Australia, the prevalence rate for vascular and mixed dementia is 13% and 28% respectively [55]. The prevalence rate of dementia is 9 times higher in patients who have had a stroke than in controls. One year after a stroke, 25% of patients develop new-onset dementia. Within 4 years following a stroke, the relative risk of incident dementia is 5.5%. The prevalence of Vascular dementia is higher in men than in women [56].

Etiology

The risk factors for VaD are from vascular causes. They include hypertension, smoking, hypercholesterolemia, diabetes mellitus, and cardiovascular and cerebrovascular disease. Several causes and presentations of VaD have clinical value. Perhaps the most obvious patients are those who meet criteria for dementia and have sustained a clinical stroke, either large artery (usually cortical)

or small artery (lacunes) in subcortical areas. Strokes are usually confirmed by neuroimaging that demonstrates either multiple infarcts or a single strategically placed infarct (e.g., angular gyrus, thalamus, brain forebrain, posterior cerebral artery, or anterior cerebral artery). In this field, MRI is more sensitive than CT [57].

It was mentioned before that the risk factors of Vascular dementia are vascular causes. These may be influenced by many other factors. Some of the most important factors that can lead to the development of dementia are older age, lower education level, family history of dementia, left-sided lesions, larger lesions, larger periventricular white matter ischemic lesions and strokes in thalamic artery territory, inferomedian temporal lobes, hippocampus, and watershed infarcts involving superior frontal and parietal regions [57].

Pathophysiology

VaD has many subtypes. The following subtypes of Vascular dementia have been described to date. The spectrum includes (a) mild vascular cognitive impairment, (b) multi-infarct dementia, (c) vascular dementia due to a strategic single infarct, (d) vascular dementia due to lacunar lesions, (e) vascular dementia due to hemorrhagic lesions, (f) Binswanger disease, (g) subcortical vascular dementia, and (h) mixed dementia (combination of AD and vascular dementia) [56].

The vascular causes of the VaD are vascular diseases. These produce either focal or diffuse effects on the brain and cause cognitive decline. The focal cerebrovascular disease occurs secondary to thrombotic or embolic vascular occlusions. Common areas of the brain associated with cognitive decline are the white matter of the cerebral hemispheres and the deep gray nuclei, especially the striatum and the thalamus. Hypertension is the major cause of diffuse disease, and in many patients, both focal and diffuse diseases are observed together. The three most common mechanisms of Vascular dementia are multiple cortical infarcts, a strategic single infarct, and small vessel disease [56].

Diagnosis

The diagnosis of Vascular dementia may be complemented with the Hachinski Ischemic Score, a clinically useful tool for distinguishing Vascular dementia from Alzheimer's disease [57]. This score was described in the Alzheimer section above, and it was mentioned that a score of 7 or higher suggests Vascular dementia and a score of 4 or less suggests Alzheimer's disease. Patients with VaD commonly have mood and behavioral changes. In some patients with lacunar state and Binswanger disease, such problems may be more prominent than intellectual deficits. Executive functioning deficits are seen prior to severe memory loss in the early stages of subcortical vascular cognitive impairment [58].

For the diagnosis of VaD, several specific diagnostic criteria can be used, including the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5*)* criteria, the International Classification of Diseases, Tenth Edition criteria, the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria, the Alzheimer's Disease Diagnostic and Treatment Center criteria, and the Hachinski Ischemic Score [58].

Patients with Vascular dementia have poorer verbal fluency and more perseverative behavior compared to patients with AD. They may even have other signs of executive dysfunction such as cognitive slowing, difficulty in shifting sets, and problems with abstraction. Commonly used mental status tests include the Folstein Mini-Mental State Examination and the Cognitive Abilities Screening Instrument [59]. Neuropsychological findings vary with the site and severity of cerebrovascular disease.

Laboratory tests should be performed to rule out other causes of dementia. These laboratory tests are very important; they should routinely include a CBC count, erythrocyte sedimentation rate, glucose level, renal and liver function tests, serologic tests for syphilis, vitamin B-12 and red blood cell folate levels, and thyroid function tests [56]. Neuroimaging studies are other important biomarkers to use. They may include CT brain scanning and MRI of the

brain. The absence of cerebrovascular lesions on CT scanning or MRI is evidence against vascular etiology. The features on CT scanning or MRI that are suggestive of Vascular dementia are bilateral multiple infarcts located in the dominant hemisphere and limbic structures, multiple lacunar strokes, or periventricular white matter lesions extending into the deep white matter [56].

Health professionals can perform a Mini-Mental Status Exam (MMSE) [47], depression assessment screening using *DSM-5* criteria [60], the Geriatric Depression Scale (GDS) [61], or the Cornell Scale for Depression in Dementia [62]. They should also assess for suicidal and homicidal risk, if necessary. Health professionals can directly ask patients about suicidal or homicidal ideation (thoughts), intent, or plan.

There is another condition to consider, mild cognitive impairment (MCI). Patients with vascular MCI, which is a prodromal stage for subcortical vascular dementia, have MRI features that differ from patients with amnestic MCI, which is the prodromal stage for AD. Vascular MCI shows more extensive white matter lacunar infarcts and leukoaraiosis and minimal hippocampal and entorhinal cortical atrophies, whereas the opposite is true for amnestic MCI.

Functional imaging may also be used for diagnosis. According to a 2000 study by Nagata et al. [63] in 2000, positron emission tomography may be useful for differentiating Vascular dementia from AD. Hypoperfusion and hypometabolism can be observed in the frontal lobe, including the cingulate and superior frontal gyri, in patients with Vascular dementia. Parietotemporal pattern is observed in patients with AD. Starkstein et al. in 1996 and other authors have demonstrated that single-photon emission CT scanning produce similar findings [64].

Another evaluation that occasionally is performed in VaD is cerebral angiography, but this is performed before carotid artery surgery. It is also useful in cases of possible cerebral vasculitis; cerebral vessels can demonstrate beading. Tests that may be useful for evaluation of stroke and in certain cases of Vascular dementia include the following: echocardiography, Holter monitoring and carotid duplex Doppler scanning.

Treatment

The most important treatment in Vascular dementia is prevention. The prevention of new strokes is an example. The treatment could include administering antiplatelet drugs and controlling major vascular risk factors. Aspirin has also been found to slow the progression of VaD. Treatment of risk factors such as hypertension, hypercholesterolemia, and diabetes mellitus are very important.

The prescription of neuroprotective drugs such as nimodipine, propentofylline, and posatirelin are currently under study and may be useful for Vascular dementia. Nicardipine is a dihydropyridine calcium channel blocker that was studied for the treatment of cognitive deterioration of vascular origin. Preliminary studies showed a decrease in cognitive deterioration in patients with cerebrovascular disease. Increasing evidence supports the involvement of the cholinergic system in Vascular dementia, similar to that seen in Alzheimer dementia. However, no cholinesterase inhibitors have been approved to date for the treatment of Vascular dementia, despite positive results in clinical trials with this medication [64].

The conditions of agitation and psychosis are common in elderly patients with dementia and are challenging to manage. Even if antipsychotics have a "black-box" warning with dementia by FDA, in some countries antipsychotics are prescribed for monitoring psychotic symptoms, with a successful result. Relatively few studies have examined the use of antidepressants for the treatment of agitation and psychosis in dementia. However, the selective serotonin reuptake inhibitors (SSRIs) sertraline and citalopram appear to be associated with a reduction in symptoms of agitation when compared with placebo [65].

Differences DSM IV Versus DSM V

The need for a classification of mental disorders is very important. This has been clear throughout the history of medicine, but until recently there was little agreement on which disorders should be included and the optimal method for their organization [11]. The history of classification is

too extensive to be summarized here. We will not display here those aspects that have led directly to the development of the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* and to the mental disorders sections in the various editions of the *International Classification of Diseases (ICD)* [11], the reason being that the present summary will focus only on the DSM-IV and DSM-V and their descriptions of dementia.

DSM-IV

DSM–IV was published in 1994. It was the culmination of a 6-year effort that involved more than 1,000 individuals and numerous professional organizations. Developers of DSM–IV and the 10th edition of the ICD worked closely to coordinate their efforts, resulting in increased congruence between the two systems and fewer meaningless differences in wording. ICD–10 was published in 1992 [11]. The International Classification of Diseases (ICD-11) will be published in 2017.

Alzheimer's disease dementia, according to the criteria of the DSM-IV, is a syndrome that may be characterized by multiple cognitive deficits. They include memory impairment and at least one of the following: aphasia, apraxia, agnosia, or disturbance in executive functioning. Social or occupational function is also impaired. A diagnosis of dementia should not be made during the course of a delirium. A dementia and a delirium may both be diagnosed if the dementia is present at times when the delirium is not present [65].

DSM-V

At the beginning of 2000, for the fifth major revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM–V), work groups were formed creating a research agenda. These work groups generated hundreds of white papers, monographs, and journal articles, providing the field with a summary of the state of the science relevant to psychiatric diagnosis and indicating where gaps existed in the current research, with hopes that more emphasis would be placed on research within those areas. Afterwards, in 2007, APA formed the DSM–5 Task Force to begin revising the manual, as well as 13 work groups focusing on various disorder areas. In 2013, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition was released, replacing the term dementia with major neurocognitive disorder and mild neurocognitive disorder. The new terms focus on a decline, rather than a deficit, in function [11].

The first point to consider when the differences are described is the categories criteria. The American Psychiatric Association published DSM-V, and the DSM-IV category "Dementia, Delirium, Amnestic, and Other Cognitive Disorders" has undergone extensive revision. DSM-V has renamed this category as "Neurocognitive Disorders" (NCD), which now covers three entities: delirium, major neurocognitive disorders, and mild neurocognitive disorders. The DSM-IV version of mild NCD resembles the DSM-V version in name only. DSM-IV defined mild NCD based on a single criterion, whereas DSM-5 defines mild NCD by using several cognitive and related criteria. The main difference between mild NCD and the Key International Symposium criteria of mild cognitive impairment (MCI) is that the research work that led to the construct of MCI primarily involved elderly study participants (even though age was not part of the definition of MCI), whereas mild NCD includes acquired cognitive disorders of all age groups. DSM-V essentially discusses the epidemiology and diagnostic markers of mild NCD by drawing congruence between MCI and mild NCD [66].

Another important contribution of DSM-V is its elimination of the obligatory requirement to have memory impairment in the diagnosis of any type of dementia. For example, memory impairment was a necessary criterion for the DSM-IV diagnosis of Vascular dementia, whereas in DSM-V, the obligatory requirement for involvement of the memory domain is eliminated. DSM-V has thus rectified the "Alzheimer's-centric" criteria of DSM-IV. DSM-V also introduced additional cognitive domains that were

not present in DSM-IV: complex attention and social cognition (in addition to the DSM-IV domains of language, memory, executive function, and visuospatial function). DSM-IV used categories that described cortical lesions such as aphasia, apraxia, and agnosia as cognitive disturbances, but DSM-V has eliminated these terms, and instead listed cognitive domains (i.e., complex attention, executive function, learning and memory, language, and perceptual-motor and social cognition) [67]. DSM-V also described another weakness of DSM-IV, the absence of criteria to objectively assess cognitive decline, by using neuropsychological testing. In DSM-V, the following criterion is added: "A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing" [67].

There is another major change related to a substantial revision of "cognitive disorder not otherwise specified." This DSM-IV category undergoes marked change in order to further elaborate mild NCD, which also includes MCI [67].

One of the great benefits of the "mild NCD" definition is that it offers a more structured diagnostic approach. First, the clinician needs to decide whether the cognitive impairment is mild or major NCD. The next step is to identify possible etiology, and the last step is to document the presence or absence of behavioral symptoms [66].

In addition, the DSM-V definition of mild NCD is developed on four criteria and two specifiers. The four criteria refer to cognitive changes, functional activities, and exclusion of delirium and competing mental disorders. The two specifiers are the presumed etiologies of mild NCD and the presence or absence of behavioral problems. While the category "mild NCD" may improve reliability of diagnoses, it has yet to withstand scientific scrutiny to be considered a valid construct [67].

When mild cognitive impairment (MCI) is described, it is considered to be a transition state between normal cognition and dementia. The subtypes of MCI are highly heterogeneous in terms of etiology, presentation, and prognosis. Patients with the amnestic subtype of MCI are at high risk of progression to Alzheimer's disease (AD). This subtype may represent the prodromal stage of AD. Moreover, patients with MCI who are not aware of their memory deficits, and in whom practice effects are not observed, exhibit parietotemporal hypoperfusion on single photon emission CT, indicating that these findings are predictors of progression to AD.

In this review, one source of debate and argument to be considered is age. Some people argue that one of the main reasons for replacing the terms "dementia" and "MCI" with "major NCD" and "mild NCD" is that both dementia and MCI are associated with acquired geriatric disorders, whereas major and mild NCD are acquired cognitive disorders of all age groups. This classification, however, may potentially lead to "lumping" together different diseases. For example, a 20-year-old football player with concussion and cognitive problems could be diagnosed with mild NCD (due to traumatic brain injury). A person aged 80 years with insidious onset and gradually progressing cognitive decline, and who has minimal loss of independence, could also be diagnosed with mild NCD (due to AD) [68].

By definition, mild cognitive impairment (MCI) is considered to be a transition state between normal cognition and dementia. The subtypes of MCI are highly heterogeneous in terms of etiology, presentation, and prognosis. Patients with the amnestic subtype of MCI are at a high risk of progression to Alzheimer's disease (AD). This subtype may represent the prodromal stage of AD [69]. In order to meet the DSM-V criteria for AD, the individual must meet the criteria for major or mild neurocognitive disorder, and there should be insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired). The individual must also meet criteria for either probable or possible AD as outlined in DSM-V [70].

This new diagnosis includes both the dementia and amnestic disorder diagnoses from DSM-IV. Also, DSM-5 recognizes specific etiologic subtypes of neurocognitive dysfunction, such as Alzheimer's disease, Parkinson's disease, HIV infection, Lewy body disease, and Vascular disease. Each subgroup can be further divided into

mild or major degrees of cognitive impairment on the basis of cognitive decline, especially the inability to perform functions of daily living independently. In addition, a subspecifier "with" or "without behavioral disturbances" is available [70].

With regard to Vascular dementia, DSM-V categorizes it as an etiological subtype of either major or mild neurocognitive disorder. A summary of the DSM-V diagnostic criteria is as follows [58]: evidence of modest (mild) or significant (major) cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, and perceptual-motor or social cognition). It may be based on: (1) concern of the individual, a knowledgeable informant, or the clinician that there has been a decline in cognitive function, and (2) an impairment in cognitive performance (modest or significant) documented by standardized testing or another qualified assessment. The symptoms are not better explained by another brain disease or systemic disorder.

Probable vascular neurocognitive disorder is diagnosed if one of the following is present: (1) clinical criteria are supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease, (2) the neurocognitive syndrome is temporarily related to one or more documented cerebrovascular events, or (3) both clinical and genetic evidence of cerebrovascular disease is present.

The clinical features are consistent with a vascular etiology as suggested by either of the following: (1) onset of the cognitive deficits is temporally related to one or more cerebrovascular events, or (2) evidence for decline is prominent in complex attention (including processing speed) and frontal executive functions. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits.

Possible vascular neurocognitive disorder is diagnosed if the clinical criteria are met but neuroimaging is not available, and the temporal relationship of the neurocognitive syndrome with one or more cerebrovascular events is not established.

The nosologic distinctions between varying dementia etiologies should prove helpful in determining prognosis and therapeutic course. These nosologic distinctions are important so that the clinicians will be able to more clearly determine whether the cognitive decline alone should be the focus of concern and intervention, or whether behavioral disturbances should also be considered and addressed [71]. In addition, a mild degree of cognitive impairment is consistent with recent research suggesting that treatments for declining cognition may be phase-specific, with certain medications and approaches possibly only working early in the course of the disease. DSM-V gives an objective distinction between mild and major impairment, and this is very helpful for the clinician.

Mild neurocognitive disorder requires "modest" cognitive decline which does not interfere with "capacity for independence in everyday activities" such as paying bills or taking medications correctly. Cognitive decline meets the "major" criteria when "significant" impairment is evident or reported, and when it does interfere with a patient's independence to the point that assistance is required. The diagnostic distinction depends heavily on observable behaviors [71]. It is important to mention that mild neurocognitive disorder goes beyond normal issues of aging. It describes a level of cognitive decline that requires compensatory strategies and accommodations to provide help in maintaining independence and performing activities of daily living. When it is diagnosed as a disorder, there must be changes that impact cognitive functioning. These symptoms are usually observed by the individual, a close relative, or other knowledgeable informant, such as a friend, colleague, or clinician, or they are detected through objective testing [60].

There is a great clinical need to recognize individuals who need care for cognitive issues that go beyond normal aging. The impact of these problems is evident, but clinicians have lacked a reliable diagnosis by which to assess symptoms or understand the most appropriate treatment or services. Recent studies suggest that identifying mild neurocognitive disorder as early as possible may allow interventions to be more effective [71].

Optimistically, this new classification system will stimulate in many areas. One of the important areas is research, research in the areas of prevention and early intervention of neurocognitive disorders with physicians and mental health professionals.

Conclusion

Alzheimer's disease and Vascular dementia are the first and second most common dementias worldwide. Dementia diagnosis describes the biomarkers for screening and treatment. The new DSM-V classification provides new features and concepts, such as major and mild neurocognitive disorder instead of dementia as described by the DSM-IV. It is very important for physicians and mental health professionals to know the differences between the two classifications when aiming to improve their assessment, knowledge, and clinical practice with dementing elderly patients in their clinical settings. Additionally, the new classification stimulates research in the prevention and early intervention of neurocognitive disorders. Prevention is the best choice for treatment right now.

References

1. WHO Outlines Global Dementia Research Priorities. [Internet] Medscape. [updated 2016; cited 2016 Sep 2] Available from: www.medscape.com/viewarticle/866984.
2. Sonnen JA, Larson EB, Crane PK, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol. 2007;62(4):406–13. [Medline].
3. White L, Petrovitch H, Hardman J, et al. Cerebrovascular pathology and dementia in autopsied Honolulu–Asia Aging Study participants. Ann N Y Acad Sci. 2002;977:9–23. [Medline].
4. Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology. 2006;66(12):1837–44. [Medline].
5. Knopman DS, Parisi JE, Salviati A, et al. Neuropathology of cognitively normal elderly. J Neuropathol Exp Neurol. 2003;62(11):1087–95. [Medline].
6. Stern Y. Cognitive reserve and Alzheimer disease. Alzheimer Dis Assoc Disord. 2006;20(3 Suppl 2): S69–74. [Medline].
7. Roman GC. The epidemiology of vascular dementia. Handb Clin Neurol. 2008;89(3rd series):639–58.
8. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. Arch Neurol. 1975;32:632–7.
9. Leel-Ossy L. Data on the clinical pathology of vascular dementia. Orv Hetil. 1995;136(31):1651–7. Review. Hungarian.
10. Arevalo-Rodriguez I, Segura O, Solà I, Bonfill X, Sanchez E, Alonso-Coello P. Diagnostic tools for Alzheimer's disease dementia and other dementias. BMC Neurol. 2014;14:183.
11. American Psychiatry Association [Internet]. Arlington: [updated 23 Aug 2016; cited 2 Sep 2016]. Available from: https://www.psychiatry.org/psychiatrists/practice/dsm/dsm-5.
12. Maurer K, Maurer U. Alzheimer: the life of a physician and career of a disease. New York: Columbia University Press; 2003.
13. Alzheimer A. Uber eine eigenartige Erkangkung der Hirnrinde. Allgemeine Zeitschrift fur Psychiatrie und Psychisch–Gerichtliche Medizin. 1907;64:146–8.
14. Lakhan SE, Chawla J. Alzheimer Disease. Medscape Medical News. August 16, 2016.
15. Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2015;86(12):1299–306. [Medline].
16. Rocchi A, Orsucci D, Tognoni G, Ceravolo R, Siciliano G. The role of vascular factors in late-onset sporadic Alzheimer's disease. Genetic and molecular aspects. Curr Alzheimer Res. 2009;6(3):224–37. [Medline].
17. S Roriz-Filho J, Sá-Roriz TM, Rosset I, Camozzato AL, Santos AC, Chaves ML, et al. (Pre) diabetes, brain aging, and cognition. Biochim Biophys Acta. 2009;1792(5):432–43. [Medline].
18. Naderali EK, Ratcliffe SH, Dale MC. Obesity and Alzheimer's disease: a link between body weight and cognitive function in old age. Am J Alzheimers Dis Other Demen. 2009;24(6):445–9. [Medline].
19. de la Monte SM. Insulin resistance and Alzheimer's disease. BMB Rep. 2009;42(8):475–81. [Medline].
20. Breitner JC, Wyse BW, Anthony JC, Welsh-Bohmer KA, Steffens DC, Norton MC, et al. APOE-epsilon4 count predicts age when prevalence of AD increases, then declines: the Cache County Study. Neurology. 1999;53(2):321–31. [Medline].
21. Vemuri P, Wiste HJ, Weigand SD, Knopman DS, Shaw LM, Trojanowski JQ, et al. Effect of apolipoprotein E on biomarkers of amyloid load and neuronal pathology in Alzheimer disease. Ann Neurol. 2010;67(3):308–16. [Medline]. [Full Text].
22. Goldbourt U, Schnaider-Beeri M, Davidson M. Socioeconomic status in relationship to death of vascular disease and late-life dementia. J Neurol Sci. 2007;257(1–2):177–81. [Medline].
23. McDowell I, Xi G, Lindsay J, Tierney M. Mapping the connections between education and dementia. J Clin Exp Neuropsychol. 2007;29(2):127–41. [Medline].
24. Szekely CA, Zandi PP. Non-steroidal anti-inflammatory drugs and Alzheimer's disease: the epidemiological evidence. CNS Neurol Disord Drug Targets. 2010;9(2):132–9. [Medline].

25. Goldman JS, Hahn SE, Catania JW, LaRusse-Eckert S, Butson MB, Rumbaugh M, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. 2011;13(6):597–605. [Medline]. [Full Text].
26. Hollingworth P, Harold D, Sims R, et al. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nat Genet. 2011;43(5):429–35. [Medline]. [Full Text].
27. Caselli RJ, Dueck AC. APOE varepsilon2 and presymptomatic stage Alzheimer disease: how much is not enough? Neurology. 2010;75(22):1952–3. [Medline].
28. Chiang GC, Insel PS, Tosun D, et al. Hippocampal atrophy rates and CSF biomarkers in elderly APOE2 normal subjects. Neurology. 2010;75(22):1976–81. [Medline].
29. Finch CE, Morgan TE. Systemic inflammation, infection, ApoE alleles, and Alzheimer disease: a position paper. Curr Alzheimer Res. 2007;4(2):185–9. [Medline].
30. Anderson P. Hypertension interacts with APOE epsilon 4 to increase amyloid load. Available at http://www.medscape.com/viewarticle/781430. Accessed 8 Apr 2013.
31. Rodrigue KM, Rieck JR, Kennedy KM, Devous MD, Diaz-Arrastia R, Park DC. Risk factors for ß-amyloid deposition in healthy aging: vascular and genetic effects. JAMA Neurol. 2013:1–7. [Medline].
32. Saczynski JS, Beiser A, Seshadri S, Auerbach S, Wolf PA, Au R. Depressive symptoms and risk of dementia: the Framingham Heart Study. Neurology. 2010;75(1):35–41. [Medline]. [Full Text].
33. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82(4):239–59. [Medline].
34. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Biol. 2011;3(9):a006189. [Medline].
35. Jack Jr CR, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, 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(3):257–62. [Medline]. [Full Text].
36. 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(3):280–292. [Medline].
37. Albert MS, Dekosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, 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(3):270–9. [Medline].
38. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, 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(3):263–9. [Medline].
39. Rabinovici GD, Furst AJ, O'Neil JP, Racine CA, Mormino EC, Baker SL, et al. 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. Neurology. 2007;68(15):1205–12. [Medline].
40. Anderson P. New guidelines for amyloid PET imaging. Available at http://www.medscape.com/viewarticle/778274. Accessed 5 Feb 2013.
41. Choi SR, Schneider JA, Bennett DA, Beach TG, Bedell BJ, Zehntner SP, et al. Correlation of amyloid PET ligand florbetapir F 18 binding with Aß aggregation and neuritic plaque deposition in postmortem brain tissue. Alzheimer Dis Assoc Disord. 2012;26(1):8–16. [Medline]. [Full Text].
42. Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, et al. Use of florbetapir–PET for imaging beta-amyloid pathology. JAMA. 2011;305(3):275–83. [Medline].
43. Fleisher AS, Chen K, Liu X, Roontiva A, Thiyyagura P, Ayutyanont N, et al. Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. Arch Neurol. 2011;68(11):1404–11. [Medline].
44. US Food and Drug Administration (FDA). FDA approves second brain imaging drug to help evaluate patients for Alzheimer's disease, dementia [press release]. 2013. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm372261.htm. Accessed 25 Oct 2013.
45. Neuraceq (florbetaben F 18) prescribing information. [package insert]. Matran: Piramal Imaging, S.A; 2014.
46. Brooks M. Memory tests plus brain scans detect earliest stages of AD. Medscape Medical News. 2013. [Full Text].
47. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98. [Medline].
48. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–9.
49. Teng E, Ringman JM, Ross LK, et al. Diagnosing depression in Alzheimer disease with the national institute of mental health provisional criteria. Am J Geriatr Psychiatry. 2008;16(6):469–77. [Medline]. [Full Text].
50. Winslow BT, Onysko MK, Stob CM, Hazlewood KA. Treatment of Alzheimer disease. Am Fam Physician. 2011;83(12):1403–12. [Medline].
51. Massoud F, Léger GC. Pharmacological treatment of Alzheimer disease. Can J Psychiatry. 2011;56(10):579–88. [Medline].
52. Madhusoodanan S, Shah P, Brenner R, Gupta S. Pharmacological treatment of the psychosis of

Alzheimer's disease: what is the best approach? CNS Drugs. 2007;21(2):101–15. [Medline].
53. Freitas C, Mondragón-Llorca H, Pascual-Leone A. Noninvasive brain stimulation in Alzheimer's disease: systematic review and perspectives for the future. Exp Gerontol. 2011;46(8):611–27. [Medline].
54. Rolland Y, Abellan van Kan G, Vellas B. Healthy brain aging: role of exercise and physical activity. Clin Geriatr Med. 2010;26(1):75–87. [Medline].
55. Honea RA, Thomas GP, Harsha A, Anderson HS, Donnelly JE, Brooks WM, et al. Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer disease. Alzheimer Dis Assoc Disord. 2009;23(3):188–97. [Medline]. [Full Text].
56. Alagiakrishnan K, Ahmed I. Medscape Medical News. January 12, 2015.
57. Reuben DB. What is Vascular Dementia? Medscape Medical News. July 15, 2015.
58. Zhang-Nunes SX, Maat-Schieman ML, van Duinen SG, Roos RA, Frosch MP, Greenberg SM. The cerebral beta-amyloid angiopathies: hereditary and sporadic. Brain Pathol. 2006;16(1):30–9. [Medline].
59. Price CC, Jefferson AL, Merino JG, Heilman KM, Libon DJ. Subcortical vascular dementia: integrating neuropsychological and neuroradiologic data. Neurology. 2005;65(3):376–82. [Medline]. [Full Text].
60. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
61. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1983;17:37–49.
62. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell scale for depression in dementia. Biol Psychiatry. 1988;23(3):271–84. [Medline].
63. Nagata K, Maruya H, Yuya H, et al. Can PET data differentiate Alzheimer's disease from vascular dementia? Ann N Y Acad Sci. 2000;903:252–61. [Medline].
64. Starkstein SE, Sabe L, Vazquez S, et al. Neuropsychological, psychiatric, and cerebral blood flow findings in vascular dementia and Alzheimer's disease. Stroke. 1996;27(3):408–14. [Medline].
65. American Psychiatric Association. Practice guideline for the treatment of patients with Alzheimer's disease and other dementias of late life. American Psychiatric Association. Am J Psychiatry. 1997;154(5 Suppl):1–39. [Medline].
66. Stokin GB, Krell-Roesch J, Petersen R, Geda YE. Mild neurocognitive disorder: an old wine in a new bottle. Harv Rev Psychiatry. 2015;23(5):368–76.
67. Rabins PV, Lyketsos CG. A commentary on the proposed DSM revision regarding the classification of cognitive disorders. Am J Geriatr Psychiatry. 2011;19:201–4. [PubMed].
68. Ganguli M. Can the DSM-5 framework enhance the diagnosis of MCI? Neurology. 2013;81:2045–50. [PMC free article] [PubMed].
69. Shimizu S, Hanyu H. Mild cognitive impairment. Nihon Rinsho. 2016;74(3):455–8.
70. American Psychiatric Association. Neurocognitive disorders. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013. p. 611–4.
71. Stetka BS, Christoph U, Correll MD. A guide to DSM-5. Medscape. 2013;167:1–3.