# UPDATE ON ALZHEIMER'S DISEASE

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**Disclosure:** The author has declared no conflicts of interest.
**Received:** 17.12.14 **Accepted:** 13.02.15
**Citation:** EMJ Neurol. 2015;3[1]:82-90.

## ABSTRACT

With the disproportionate growth of the elderly population, Alzheimer's disease (AD), as the most common cause of dementia, has become a major public health and socio-economic problem of our time. Updated consensus criteria for clinical diagnosis and new biomarkers have increased the diagnostic accuracy to over 90%, with a sensitivity versus other dementias of around 85% and a specificity of up to 78%, although a definite diagnosis depends on neuropathological examination. However, due to overlap between dementing disorders and frequent concurrence of multiple pathologies in the aged brain, both clinical and post-mortem studies entail biases that affect their validity. Harmonised interdisciplinary approaches are required to increase the accuracy and reproducibility of AD diagnosis as a basis for neuroprotection and efficient treatment. Preventative measures can minimise risk factors and confounding diseases, whereas anti-dementive treatment with drugs and non-pharmacological interventions can currently only delay the progression of the clinical course without causal effects. Better early diagnosis, active immunotherapies, and disease-modifying measures are the most important challenges for modern neurosciences.

Keywords: Alzheimer's disease (AD), dementia, neuropathology, biomarkers, treatment.

## INTRODUCTION

Alzheimer's disease (AD) is a form of neurocognitive disorder characterised by a progressive multi-domain cognitive impairment with a profound decrease in the ability to perform daily living activities.[1] AD is the most frequent form of dementia (around 60% of cases), followed by dementia with Lewy bodies (DLB) (15-30%), vascular dementia/cognitive impairment, and other dementia processes (10-15% each); most frequent are mixed forms or multi-aetiology dementias (50-70%).[2] AD affects more than 40 million people worldwide. The principal risk factor is age: its incidence doubles every 5 years after age 65, and the odds for a diagnosis of AD after age 85 exceed one in three. With the disproportionate growth of the elderly population, the prevalence of AD is predicted to approach around 115 million worldwide in 2050.[3] The total costs for AD in 2013 were approximately US$205 billion in the USA alone and about US$605 billion worldwide, not including the contributions of unpaid caregivers.[4,5] Thus, AD has become a major public health and socio-economic problem that threatens to become the scourge of the 21st century. The clinical and neuropathological diagnosis of AD, as well as the current and future treatment options, are the focus of the present mini-review.

## CLINICAL DIAGNOSIS

Early diagnosis of AD and its distinction from other dementing disorders is crucial to the implementation of effective treatment strategies and management of patients. Diagnostic procedures play a major role in the detection of preclinical AD and mild cognitive impairment (MCI).[6] Diagnosis of MCI requires a cognitive complaint or evidence for longitudinal decline (at least 1.5 standard deviations) on cognitive test performance, generally intact global cognition, minimal or no functional impairment, and no dementia according to DSM-IV criteria. The different subtypes of MCI include amnestic and non-amnestic single and multi-domain forms. Progression to dementia has been reported in 10-15% of cases per year, while others may not progress to AD or

other dementias.[7] MCI, being common in elderly people (average prevalence: 20-30%), is associated with future cognitive decline and progression to dementia in 90% of cases within 9-10 years (10-15% of cases per year) as opposed to the 1-2% incidence in age-matched general populations.[8] For its diagnosis, several stages were proposed (Figure 1a),[9] by which 97% of cognitively normal persons were classified.[10] The pathology and mechanisms of MCI were summarised recently.[11]

Updated consensus criteria for the clinical diagnosis of AD include the revised National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) guidelines, the National Institute on Aging-Alzheimer's Association (NIA-AA), and European Federation of Neurological Societies – European Neurological Society (EFNS-ENS) guidelines,[12] consensus from the Canadian Conference on the Diagnosis of Dementia (CCCD), and the International Working Group-2 criteria for AD.[13] All these updated diagnostic criteria considering clinical phenotypes, preclinical states and mixed AD, adequate neurophysiological/cognitive assessment, neuropsychological testing, cerebrospinal fluid (CSF) biomarkers (decreased β-amyloid [Aβ], increased phospho-tau [p-tau], p-tau/Aβ42 ratio >0.52 – a robust marker for AD), and neuroimaging procedures (volumetric and functional magnetic resonance imaging [MRI] demonstrating early and progressive hippocampal and parietal atrophy in mixed AD and AD,[14-16] fluorodeoxyglucose positron emission tomography [PET], amyloid detection by $^{11}$C-labelled Pittsburgh Compound-B PET) increase the clinical diagnostic accuracy to about 95%.

Combining the best CSF and MRI data using standardised operational measures allows for a more precise diagnostic prediction, and will be further increased by using multimodal techniques and novel biomarkers already in the early (preclinical) stages of development.[17-22] A large proportion of cognitively normal elderly people develop Aβ pathology 5-10 years before disease manifestation, but there are conflicting results with biomarker changes and disease progression. Therefore, longitudinal biomarker evidence is needed.[23] Meanwhile, the advances in tau imaging will enable better identification of AD.[24] The current definition of AD is given in Table 1.[25,26] The diagnostic criteria for AD have been revised recently as follows:[27]

- Definition of dementia concerns essential entities (AD, DLB, vascular dementia, frontotemporal dementia, prion disorders)
- Classical definition of MCI fills gap between cognitively normal state and dementia
- Contains central points of the NICDS-ADRDA criteria
- Biomarkers (CSF, serum protein, neuroimaging) as parts of expanded criteria are necessary
- Quantitative clinical and pathological criteria to be used together with disease categories

Meta-analysis of several sets of autopsy cases from the National Alzheimer's Coordinating Center Registry USA revealed a higher diagnostic accuracy for AD (sensitivity of 71-85% and specificity of 44-78%), with both values being slightly better for imaging procedures than for CSF markers. However, the data varied due to heterogeneity of the study designs.[28,29]

## NEUROPATHOLOGICAL DIAGNOSIS

AD is a neurodegenerative disorder with a well-defined neuropathological background characterised by the accumulation of tau protein within neurons (neurofibrillary tangles [NFTs]) and the extracellular deposition of Aβ (plaques, amyloid angiopathy) in the brain parenchyma, which is associated with neuronal and synaptic loss.[30] The histopathological examination of the brain using modern molecular-biological methods under standardised conditions still represents the 'gold standard' for AD diagnosis, although the frequent overlap of various processes and multimorbidity of the ageing brain have to be considered.[31-33] The current algorithms for the neuropathological diagnosis of AD are based on the assessment of senile plaques and NFTs, providing inter-rater agreement when using standardised criteria.

Guidelines for the neuropathological diagnosis of AD include quantitative cut-off values for plaques and tangles, their semi-quantitative assessment and age-adjustment (Consortium to Establish a Registry for Alzheimer's Disease [CERAD] protocol), topographic staging of neuritic/tau pathology (Braak staging), and the progress and distribution of Aβ deposition, which differs from tau pathology. The recent NIA-AA guidelines consider AD pathology regardless of the clinical history of a given individual. They include: (i) the recognition that AD pathology may occur in the absence of cognitive impairment; (ii) an 'ABC'

score of AD pathology that incorporates assessment of amyloid plaques (A), staging of tangles based on the Braak staging system (B), and scoring of neuritic plaques based on semi-quantitative assessment in at least five neocortical regions (C), based on CERAD criteria (Figure 1b);[34-37] and (iii) more detailed approaches for assessing comorbid conditions, such as DLB or vascular pathology.

Preliminary testing of the revised NIA-AA guidelines distinguished AD from non-demented cases with a sensitivity of 71% and a specificity of 99%. However, there is growing appreciation, not yet incorporated into these guidelines, that the neuropathology of AD is heterogeneous and includes a number of subtypes, e.g. limbic-predominant, hippocampal-sparing, and typical forms,[38] and primary age-related tauopathy (PART), previously referred to as 'tangle-only dementia',[39] without evidence of Aβ accumulation.[40] Further diagnostic challenges include the fact that neuropathology of AD in very old patients differs considerably in both intensity and distribution from younger age groups.

A.

| Stage | PIB-PET | HVa | FDG-PET | Cognitive disorder |
|---|---|---|---|---|
| 0 | - | - | - | - |
| 1 | + | - | - | - |
| 2 | + | - (+) | + (-) | - |
| 3 | + | - (+) | + (-) | + |
| SNAP | - | - (+) | + (+) | - (+) |
| Unclassified | - (+) | - | - | + |

B.

| Level of AD neuropathologic change | | | | | | |
|---|---|---|---|---|---|---|
| *Thal phase for Aβ plaques* | A | B | | | C | *CERAD* |
| | | 0 or 1 | 2 | 3 | | |
| *0* | 0 | Not | Not | Not | 0 | *neg* |
| *1 or 2* | 1 | Low | Low | Low | 0 or 1 | *neg or A* |
| *1 or 2* | 1 | Low | Intermediate | Intermediate | 2 or 3 | *B or C* |
| *3* | 2 | Low | Intermediate | Intermediate | Any C | *neg or A to C* |
| *4 or 5* | 3 | Low | Intermediate | Intermediate | 0 or 1 | *neg or A* |
| *4 or 5* | 3 | Low | Intermediate | High | 2 or 3 | *B or C* |
| | | *Braak 0-II* | *Braak III-IV* | *Braak V-VI* | | |

**Figure 1: The role of biomarkers in the diagnosis of preclinical Alzheimer's disease (AD)/mild cognitive impairment (MCI) and ABC criteria for the neuropathological diagnosis of AD.**

A: Preclinical AD stages (MCI) in cognitively normal patients using biomarkers with 90% sensitivity for the diagnosis of AD and 10th percentile of normal cognitive score. *Modified from Jack CR Jr et al.*[9] B: ABC criteria for the diagnosis of AD-related pathology. The level of AD neuropathological change is determined by assessing A, B, and C scores. A ('A' for amyloid) scores are related to phases of β-amyloid (Aβ) deposition (first column; described by Thal DR et al.[34]). Score 1 includes phases 1+2, score 2 = phase 3, score 3 includes phases 4+5, score 0 indicates absence of Aβ deposits. B ('B' for Braak): neurofibrillary degeneration should be assessed based on the Staging system described by Braak and Braak[35] and on tau immunohistochemistry. Score 1 includes Stages I+II (transentorhinal), score 2 includes Stages III+IV (limbic), score 3 includes Stages V+VI (isocortical), and score 0 indicates absence of neurofibrillary tau pathology. C ('C' for CERAD): evaluation of neuritic plaques is based on the semi-quantitative scoring system described by Mirra et al.[36] Score 0 indicates absence, score 1 refers to sparse, score 2 to moderate, and score 3 to frequent neuritic plaques. *Modified from Montine TJ et al.*[37] FDG: fluorodeoxyglucose; HVa: hippocampal volume; PET: positron emission tomography; PIB: Pittsburgh compound B; SNAP: suspected non-Alzheimer pathophysiology; CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

**Table 1: Definition of Alzheimer's disease (AD) dementia from the National Institute on Aging and Alzheimer's Association Workgroup.**

| **A. Probable AD dementia is diagnosed when the patient:** |
|---|
| 1. Meets criteria for dementia, and has the following characteristics:<br>2. Insidious onset. Symptoms have a gradual onset over months to years; and<br>3. Clear-cut history of worsening of cognition by report or observation; and<br>4. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:<br>a) *Amnestic disorder:* the most common syndromic presentation of AD dementia<br>b) *Non-amnestic disorders:*<br>– language disorder<br>– visuospatial disorder<br>– executive and behavioural disorder.<br>5. Exclusions: the diagnosis of probable AD dementia should not be applied when there is evidence of:<br>a) Substantial concomitant cerebrovascular disease; or<br>b) Core features of dementia with Lewy Bodies (DLB) other than dementia itself; or<br>c) Prominent features of behavioural variant frontotemporal dementia; or<br>d) Prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or<br>e) Evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or medication use that could have a substantial impact on cognition. |
| **B. Possible AD dementia is diagnosed when the patient meets one of the two following criteria:** |
| 1. *Atypical course:* meets the core clinical criteria (1) and (4) (above) for probable AD dementia, but either had a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline; or<br>2. *Aetiologically mixed presentation:* meets all core clinical criteria (1) through (4) for probable AD dementia but has evidence of:<br>a) Concomitant cerebrovascular disease; or<br>b) Features of DLB other than the dementia itself; or<br>c) Evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial impact on cognition. |
| **C. Research definition of probable AD dementia with biomarkers*** |
| 1. Meets clinical criteria (1) through (5) for probable AD dementia and has the following levels of probability of AD pathophysiology based on the profile of neuroimaging and cerebrospinal fluid (CSF) biomarkers:<br>a) Highest probability: β-amyloid marker (CSF or imaging) 'positive' and neuronal injury marker (CSF tau, FDG-PET, or structural MRI) 'positive'<br>b) Intermediate probability: β-amyloid marker 'positive' or neuronal injury marker 'positive'<br>c) Uninformative: biomarkers unavailable, conflicting, or indeterminate. |
| **D. Research definition of possible AD dementia with biomarkers*** |
| 1. Meets clinical criteria for possible AD dementia and has the following levels of probability of AD pathophysiology based on the profile of neuroimaging and CSF biomarkers:<br>a) High, but does not rule out second aetiology: β-amyloid marker 'positive' and neuronal injury marker 'positive'<br>b) Uninformative: any other configuration of biomarkers |

*A biomarker is considered 'positive' if it has a value that is regarded as diagnostic of AD pathophysiology. As of 2011, there are no universally accepted standards for what is considered diagnostic of AD pathophysiology for any of the biomarkers listed in this table. Therefore, standards based on local experience would be used.

FDG: fluorodeoxyglucose; PET: positron emission tomography; MRI: magnetic resonance imaging.

*Table modified from Knopman D,[25] data source taken from McKhann GM et al.[26]*

There is considerable overlap between demented and non-demented seniors, dementia in the oldest (90+ years) being only modestly related to AD, while cerebrovascular pathologies may cause cognitive impairment in patients with low AD pathology scores.[41,42] However, dementia lacking a known pathological background is extremely rare.[43]

**Table 2: Drug treatment of cognitive symptoms in Alzheimer's disease.**

| | Evidence classification | Efficacy | Clinical recommendation |
|---|---|---|---|
| **1. Cholinesterase inhibitors** | | | |
| Donezepil (Aricept®) | 1a | ++ | A |
| Rivastigmine (Exelon®) | 1a | ++ | A |
| Galantamine (Reminyl®) | 1a | ++ | A |
| **2. Other cognitive-enhancing drugs** | | | |
| Memantine (Axura®, Ebixa®) | 1a | ++ | A |
| Cerebrolysin® - intravenous | 1b | + | B |
| Selegiline (Jumex®, Cognitive®, Selegiline Genericon®, Xilopar®) | 2b | + | C |
| Tocopherol (vitamin E) | 1b | + | D |
| Dihydroergotoxine (Codergocrin®, Dorehydrin®, Ergomed®, Hydergine®) | 2b | +/- | D |
| Piracetam (Cerebryl®, Nootropil®, Novocephal®, Pirabene®) | 2b | +/- | D |
| Idebenone (co-enzyme Q10 derivate) | 3 | +/- | D |
| Nimodipine (Nimotop®) | 2b | +/- | D |
| Ginkgo biloba (Cerebokan®, Ceremin®, Gingel®, Tebofortan®, Tebonin ret.®) | 1a | + | B |
| Nicergoline (Ergotop®, Nicergin®, Sermion®) | 2a | + | B |
| Propentofylline | 3 | +/- | B |
| Pentoxifylline (Hemodyn®, Pentohexal®, Pentomer®, Pentoxi 'Genericon'®, Pentoximed®, Trental [Vasonit®]) | 3 | +/- | D |
| Vincamine | 3 | +/- | D |
| Substitution of oestrogen | 2b | +/-/- | D |

++ significant; + good; +/- questionable.

Evidence classification

1a: by several randomised controlled studies and/or meta-analyses. 1b: by one randomised controlled study. 2a: by one methodologically correct but not randomised study. 2b: by one methodologically correct, e.g. experimental study. Intervention without control (e.g. application study). 3: by methodologically correct, not-experimental observation studies (e.g. case reports). 4: by experimental statements.

Clinical recommendation

A: recommended with definite clinical reliability. B: recommended with moderate clinical reliability. C: recommended on the basis of individual circumstances. D: cannot be recommended according to available data.

*Modified from Schmidt et al.*[51]

Another major diagnostic problem is the frequent presence of multiple pathologies in the aged brain that coexist with AD and affect its clinical course. About two-thirds of aged human brains show non-AD type pathology, which is often missed clinically and cannot be identified without neuropathological examination.[31-33] The burden of vascular, AD type, and other pathologies are consistent with an additive or synergistic effect of these types of lesions on cognitive impairment.[41-44]

## CURRENT TREATMENT OPTIONS

Current treatment of AD patients includes: (i) drug treatment of cognitive and non-cognitive symptoms including neuropsychiatric complications;

(ii) non-pharmacological treatment options such as cognitive training and psychosocial activation; and (iii) preventive measures to reduce risk factors.

## Drug Treatment

Current first-line drugs in the treatment of AD include cholinesterase inhibitors (CHI) – donepezil (oral or transdermal application), rivastigmine, galantamine, and the N-methyl-D-aspartate receptor channel blocker memantine, or their combination. CHIs are approved for mild-to-moderate AD, whereas memantine is approved for moderate-to-severe AD. The use of a combination of CHIs plus memantine rather than CHIs alone in patients with moderate-to-severe AD has been recommended, in particular for moderately severe AD cases with behavioural symptoms.[45,46] Meta-analysis of the efficacy of these drugs showed that they are able to stabilise or slow decline in cognition, function, behaviour, and global change, with better tolerability than memantine.[47] However, like other cognitive-enhancing drugs (cerebrolysin, ginkgo biloba), they have only mild-to-moderate effects on memory and capabilities for daily living, inducing delay of progression for about 6-12 months, with stable efficacy over years.

A recent long-term study of gingko biloba extract, however, did not find significant differences compared with placebo.[48] Changes between treatments in cases of intolerance and/or inefficacy are possible. Efficient and approved pharmacological treatment options for MCI as a prodromal syndrome of AD are still lacking.[49] For a critical review of cognitive enhancers (nootropics) please refer to Froestl et al.[50] Many other treatments (hydergine, nicergoline, piracetam, pyritinol, etc.) cannot be recommended in view of indefinite efficacy (Table 2).[51] The benefit–cost ratio of AD drugs was validated cautiously as being low between drug and non-pharmacological applications. Most drugs entering the AD drug-development pipeline have failed and there exists an urgent need to increase the support of the AD drug-development ecosystem.[52] Recent studies of intravenous immunoglobulin that sequesters Aβ and was suggested to interfere with AD progression failed.[53]

Drug therapy of non-cognitive symptoms, such as depression and other neuropsychiatric complications (behavioural and psychological symptoms of dementia [BPSD]), in addition to CHIs and related drugs, includes cautious use of new antipsychotic drugs (risperidone, olanzapine, quetiapine, clozapine) and anti-depressive drugs (in particular, selective serotonin reuptake inhibitors such as sertraline and citalopram; less efficient tricyclic antidepressive drugs, which have an anticholinergic potential that is a negative feature in AD; and potentially fluvoxamine and paroxetine), the cautious use of benzodiazepines in case of anxiety and aggression, and occasionally anticonvulsive drugs (carbamazepine, valproate). CHIs and atypical antipsychotics could improve BPSD in AD patients, but with adverse safety outcomes.[54]

Non-pharmacological options include combined programmes to increase cognitive functions, behaviour, mood, daily activities, independence, and thus quality of life. Close co-operation between caregivers, family, and therapists with the patient may ameliorate their motivation and remaining capacities by activation of the cognitive reserve, as well as influence their mood. Changes in lifestyle, physical and psychological activity, and reduction of common risk factors such as hypertension, hyperlipidaemia, obesity, diabetes, and smoking are of highest priority for the prevention of AD and related processes. A slowing of disease progression until 2050 could reduce the number of cases by about 12 million.[55] AD and other dementia disorders are currently incurable but can be prevented, at least in part.

## Immunotherapies for AD

Recent advances in the understanding of AD pathogenesis have led to the development of numerous compounds that can modify the disease process. Both passive and active immunotherapies have been shown to reduce Aβ accumulation and prevent downstream pathology in animal models, indicating that intervention appears to be effective in the early stages of amyloid accumulation.[56] Several trials demonstrated by post-mortem examination and *in vivo* imaging that Aβ can be removed from the human AD brain, although this increases cerebral amyloid angiopathy.[57] The most developed method for targeting Aβ is the use of monoclonal antibodies, including bapineuzumab, solanezumab, and crenezumab, as suitable drug candidates in preventative clinical trials for AD.[58,59] However, the evidence for unequivocal cognitive benefits has been disappointing so far.[60,61]

As the aggregation and accumulation of the microtubule-associated protein tau is a

pathological hallmark of AD and other tauopathies, tau-based immunotherapy has been considered as a novel therapeutic target in AD, and a number of animal studies have shown the efficacy of both passive and active immunisation;[62,63] human trials will be performed in the future.[64] Another approach may be to combine second-generation anti-Aβ vaccines with a drug that inhibits β-site amyloid precursor protein-cleaving enzyme 1 (BACE1), which disrupts cleavage of amyloid precursor protein and Aβ formation. A combination trial in patients at risk of developing AD was announced in July 2014,[65] but BACE1 inhibitors have had a mixed track record to date.[66] Other BACE1 inhibitors are in Phase I testing.

The goal of ongoing studies is the assessment of clinical efficacy with adequate safety and tolerability, but a final judgement of the immunotherapeutic modalities and other disease-modifying procedures is impossible. Future treatment strategies using multimodal and multifunctional substances influencing causal disease processes, such as amyloid production and phosphorylation of tau protein, and their interrelation with neurodegeneration are necessary and should be applied in early/preclinical stages of the disease.

## CONCLUSION AND FUTURE DEVELOPMENT

Recent insights into the molecular pathogenesis of AD and updated clinical and neuropathological consensus criteria have increased the diagnostic accuracy and early recognition of AD. Interdisciplinary projects for the standardised assessment of clinical phenotype, neuroimaging, and biomarkers are currently under way.[27,67] Use of the updated diagnostic criteria for AD considering clinical phenotype, CSF and other biomarkers, modern neuroimaging, and multimodal techniques have increased the clinical diagnostic accuracy of AD to approximately 90%, while modern molecular, genetic, and standard laboratory methods can achieve a final diagnosis or classification in up to 96% of cases. In the majority of cases, excepting those with known genetic or metabolic background, clinical and pathological examination may not be able to clarify the causes/aetiology of AD and other dementing disorders. Therefore, the reliability and clinical relevance of the current diagnostic criteria need better qualification and validation in order to enable an early diagnosis of preclinical AD and related disorders as a basis for further neuroprotective and effective disease-modifying treatment options.[68]

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