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Alzheimer's disease – standard of diagnosis, treatment, care, and prevention

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ABSTRACT

Alzheimer's disease (AD) is the most frequent cause of dementia in people ≥ 60 years. This white paper summarizes the current standards of AD diagnosis, treatment, care, and prevention. Cerebrospinal fluid (CSF) and positron emission tomography (PET) measures of cerebral amyloidosis and tauopathy allow the diagnosis of AD even before dementia (prodromal stage) and provide endpoints for treatments aimed at slowing the AD course. Licensed pharmacologic symptomatic drugs enhance cholinergic pathways and moderate excess of glutamatergic transmission to stabilize cognition. Disease-modifying experimental drugs moderate or remove brain amyloidosis, but so far with modest clinical effects. Nonpharmacological interventions and a healthy lifestyle (diet, socio-affective inclusion, cognitive stimulation, physical exercise, etc.) provide some beneficial effects. Prevention mainly targets modifiable dementia risk factors such as unhealthy lifestyle, cardiovascular-metabolic and sleep-wake cycle abnormalities, and mental disorders. A major challenge for the future is telemonitoring in the real world of those modifiable risk factors.

EPIDEMIOLOGY AND RISK FACTORS OF ALZHEIMER'S DISEASE

Seven of the top ten causes of death include Alzheimer's disease (AD) and Related Dementias (ADRD), as well as ADRD risk factors: ischaemic heart disease, stroke, chronic obstructive pulmonary disease, and Type 2 diabetes (T2D) (*1*). There are ~55 million people with dementia. Dementia is expected to increase 42% (78 million) by 2030 and more than 250% (139 million) by 2050, mostly among women (*2*). Longitudinal associations exist between AD and overweight and obesity, hypertension, high cholesterol, low respiratory function, high blood levels of homocysteine, and co-occurring vascular comorbidities. Concomitant associations exist for vascular risk factors and AD-related brain pathologies as well as white matter hyperintensities, neurodegeneration, blood brain barrier disruption, cerebral infarcts, and various forms of cerebrovascular disease. The evidence base for AD prevention appears strongest for control of vascular risk factors. a

Other AD risk factors include environmental risk factors such as high stress, air pollution, and lack of social support; depression; and sociodemographic factors including low education, low income and social isolation (*3*). Susceptibility genes for AD support systems biology approaches for dyslipidemias, blood pressure and body weight dysregulation, type 2 diabetes, systemic- and neuroinflammation, and immune alterations.

These data provide a solid foundation for understanding the pathogenesis of Alzheimer's disease as a multifactorial process, (described in the following section), and for AD prevention strategies, (described in the last section).

AD PATHOGENESIS

The most widely-accepted view on AD pathogenesis is based on the amyloid cascade hypothesis, published in 1992 (*4*), and repeatedly revised. This hypothesis is based on the disease-defining presence of amyloid plaques in the brain at autopsy and the observation that rare cases of autosomal dominant AD are associated with mutations in amyloid-related genes encoding the amyloid precursor protein (APP) or one of the two secretases involved in APP processing, presenilin-1 and 2. The APOE epsilon4 allele is the most strongly and consistently associated risk gene for sporadic AD. It is associated with many pathogenic pathways, including increased amyloid production.

The widespread failure of amyloid-centered treatments triggered the search for a broader perspective of AD pathogenesis (*5*). In addition to amyloid, pathological phosphorylation and subsequent loss of function of the microtubule-associated protein tau, oxidative stress, impaired glucose metabolism, and upregulation of neuroinflammation play key roles in AD pathogenesis and interact with amyloid pathology. Supplementary Table 1 reports AD pathogenic events that are amenable to molecular brain imaging.

CLINICAL DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF AD

Cognitive symptoms, such as forgetfulness, or concern by family members, prompts patients to make initial contact with a primary care physician. This physician has a decisive role in the diagnostic journey of the patient. The first diagnostic step, already accessible in primary care, is medical history of the patient (self and/or per proxy), complemented by a cognitive screening test and physical examination. These clinical examinations can determine, in most cases, whether cognitive impairment or dementia is present.

One important clinical distinction is a full syndrome of dementia (i.e., cognitive impairment severe enough to impair daily activities) versus mild cognitive impairment (MCI; i.e., impairment in one of more cognitive domains with maintained global cognitive function and daily activities), versus subjective cognitive decline (SCD; i.e., cognitive complaints without impairment on cognitive tests). Both MCI and SCD are recognized as risk states for development of dementia, but most countries do not endorse specific pharmacological treatments outside of clinical trials.

The etiological diagnosis of MCI or a dementia syndrome will typically be conducted by a specialist. Diagnosis requires in-depth neuropsychological and neurological examinations, basic laboratory testing, and structural brain imaging using MRI or CT. Further diagnostic work-up may include biomarkers from PET brain imaging, cerebrospinal fluid (CSF) and (in the future) peripheral blood. Etiological diagnosis is challenging, since autopsy studies show that co-morbidities of two or more neurodegenerative proteinopathies are common.

Clinical and pathological features of AD and its differential diagnoses are reported in Supplementary Table 2. A thorough account of the AD diagnostic process is provided in the World Alzheimer Report 2021 (*6*).

Research criteria ushered in the diagnoses of prodromal and preclinical stages of AD. Based on earliest presence of MCI and positive AD biomarkers, the International Working Group-2 criteria allow diagnosis of prodromal AD (*7*). The US National Institute on Aging and Alzheimer's Association criteria endorse a diagnosis of preclinical AD with the presence of positive AD biomarkers (CSF or amyloid imaging) and the absence of cognitive impairment (*8*). These criteria have further been systematized as the A/T/N classification scheme (*9*) (Table 1).

NEUROPSYCHOLOGY

The diagnostic work-up of patients with suspected AD includes cognitive screening using, for example, the Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA). Short clinical instruments are well-suited to detect an impairment consistent with dementia, and to quantify dementia progression over time. However, neuropsychological tests of specific cognitive domains are more sensitive to early changes, and provide useful information for differential dementia diagnoses. Popular short test batteries suited for the detection and characterization of MCI are the Consortium to Establish a Registry for AD Neuropsychological Battery (CERAD-NP, (*10*)), the Uniform Data Set Test Battery of the American AD Research Centers (NACC UDS-NP, (*11*)), and the Repeatable Battery of Neuropsychological status (RBANS, (*12*)).

More recent approaches to sensitively detect cognitive decline and account for day-to-day variations in performance include continuous monitoring of cognitive performance using digital devices, such as serious games applications. Descriptions of these approaches are beyond the scope of this standard of care article, however details are available in (*13*).

BIOMARKER-BASED DIAGNOSIS

Fluid biomarkers

Several CSF biomarkers are well-established and standard for AD diagnosis. Lower CSF $A\beta_{1–42}$ and higher CSF total tau (T-tau) or phosphorylated tau (P-tau) provide in-vivo evidences of AD pathology, as integrated into the A/T/N scheme (Table 1). Lower CSF $A\beta_{1–42}$ concentration is associated with greater amyloid plaque formation (*9*). T-tau and P-tau reflect neuronal degeneration and tangle pathology, respectively (*9*). The combination of CSF markers - CSF $A\beta_{1–42}$ and T-tau or P-tau - performs better than each individually for diagnosing AD (*14*).

Since CSF collection involves lumbar puncture, this led to the search for minimally invasive blood-based biomarkers. One candidate is plasma NFL that is increased in patients with AD, and may be useful to monitor neurodegeneration, disease progression and treatment response. In addition, plasma Aβ42 and Aβ40 predict brain amyloid burden status at any stage of AD (*15*). Plasma Aβ42/Aβ40 could be used to screen for individuals likely to develop brain amyloidosis and who are at risk for AD (*16*). Furthermore, plasma P-tau181 levels are increased in AD patients compared to controls and strongly associated with both Aβ and Tau PET (*17*). Moreover, plasma P-tau217 also accurately discriminated AD from other neurodegenerative diseases, and was more accurate than other established plasma- and MRI-based biomarkers (*18*). The sensitivity and specificity of fluid biomarkers for AD are provided in Table 2.

Neuroimaging/PET biomarkers

Neuroimaging techniques provide the best opportunity to visualize and quantify neurodegenerative and molecular changes in the living human brain over the course of AD. Magnetic resonance imaging (MRI) has been included in dementia screening protocols for

decades. The most widely used MRI read to support a diagnosis of clinical AD are measures of regional brain volumes using T1-weighted images. These images are visually assessed by a trained radiologist who uses standardized rating scales to determine the level of medial temporal lobe, posterior or global brain atrophy. In addition, various forms of vascular pathology can be assessed, including white matter hyperintensities (using T2-weighted or fluid-attenuated inversion recovery [FLAIR] MRI sequences), infarcts and microhemorrhages (using susceptibility-weighted T2* MRI sequences). MRI is also used to exclude other causes of cognitive impairment such as stroke, brain tumors or multiple sclerosis.

Another established neuroimaging marker of neurodegeneration is glucose hypometabolism measured with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET). In persons with AD, FDG-PET shows a hypometabolic pattern that primarily affects the posterior cingulate, precuneus, and lateral temporal and parietal regions.

The neurodegenerative patterns observed on structural MRI and FDG-PET images show modest differential diagnostic accuracy between AD and non-AD neurodegenerative disorders (~70-80%). Neurodegenerative disorders are characterized by substantial functional and anatomical heterogeneity, hence there is substantial overlap between neurodegenerative disorders on MRI and FDG-PET. The advent of PET tracers that detect the neuropathological hallmarks of AD *in vivo* represent a genuine breakthrough in the field. The first PET tracer that could detect the presence of fibrillar amyloid-β pathology was ^{11}C-Pittsburgh compound-B (^{11}C-PIB). There is a strong association between ante-mortem ^{11}C-PIB-PET signal and post-mortem amyloid-β load (sensitivity: 92%, specificity: 97%) (*19*). PIB PET is abnormal early in the disease process, and investigational use of this tracer in the clinic shows positive changes in diagnostic confidence and patient management. Subsequently, several ^{18}F amyloid-β tracers became

available, i.e., ^{18}F-flutemetamol, ^{18}F-florbetaben and ^{18}F-florbetapir, which showed nearly similar characteristics as [^{11}C]PIB and are now approved for clinical use with a visual read metric as the method to determine amyloid-β status by, for example, the U.S. FDA and European Medical Association (EMA). The primary strength of amyloid-β tracers for diagnostic purposes is their negative predictive value. A diagnosis of AD can be ruled out with high certainty if the amyloid-β PET scan yields a negative result. A downside of this sensitivity of the amyloid-β tracers is their limited specificity. Amyloid-β positive PET scans are observed in 10-40% of the cognitively normal population, and this increases with age (*20*).

Recently, several novel tau PET tracers (e.g., ^{18}F-flortaucipir, ^{18}F-MK6240 and ^{18}F-RO948) were introduced that detect the presence of AD-like tau aggregates (i.e., a combination of 3R/4R tau in paired helical filaments) with high affinity and selectivity. In May 2020, the first tau PET tracer was approved by the U.S. FDA to support the diagnosis of suspected AD dementia. Future work regarding tau PET tracers will define optimal methodologies (i.e., visual read metrics and/or quantitative thresholds) and most appropriate use.

Supplementary section S1 expands the perspective on imaging markers to resting state EEG as a potential screening instrument for AD (*21*).

MEDICAL TREATMENT OF AD

Pharmacological treatment of clinically symptomatic AD has two major elements. The first element is critical review of the patient's current medications, particularly for potential anticholinergic side effects that impair memory and increase the risk of delirium. Other contraindicated drugs are sedatives, such as benzodiazepines, and (low-potency) antipsychotics.

Several indices are available for clinicians and pharmacists to identify potentially inappropriate medication combinations and possible alternatives (*22*).

The second element is the prescription of an antidementia drug. Supplementary Table 3 lists approved antidementia drugs with their clinical indication, major side effects, and typical dosage. None of the aforementioned drugs has convincingly shown disease-modifying effects, but all have shown symptomatic benefits with reduced rates of cognitive decline, reduction of caregiver burden and, in some studies, delayed institutionalization when compared with placebo (*23*). Of note, AD is severely underdiagnosed in primary care. Studies show that <50% of people with AD receive specific dementia drug treatment (*24,25*). There is much room for improvement.

DISEASE-MODIFYING TREATMENTS

Repeated anti-amyloid failures were a setback for patients and scientists, but they also led to sharpening inclusion criteria and an early diagnosis of AD. However, until January 2022 and including aducanumab, recently approved by the FDA, no anti-amyloid antibody therapy has successfully reached the clinical endpoint in a completed phase 3 study. Phase 3 trials are ongoing with anti-amyloid antibodies, such as gantenerumab, lecanemab, and donanemab that, in preclinical studies, selectively bound to aggregated Aβ,. These newer generation anti-amyloid antibodies have consistently shown removal of brain Aβ per amyloid PET imaging studies (*26*), and in phase 2 studies, have shown improvements in primary cognitive outcomes (*26,27*).

Aducanumab (Aduhelm®) was approved by the FDA on June 7, 2021 using the FDA's accelerated approval pathway. On December 16, 2021, the European Medicines Agency (EMA) recommended refusing the marketing authorization for aducanumab. Of note, treatment with

aducanumab was restricted by the FDA in July 2021 to prodromal and mild stages of AD with proven amyloid positivity via CSF or amyloid PET.

Non-pharmacological treatment options are described in Supplementary Section S2 (*28,29*).

AD PREVENTION AND MULTIMODAL INTERVENTIONS

It is estimated that 40% of all dementias in high-income countries could be prevented or delayed with elimination of: low early-life education; mid-life obesity, hypertension, alcohol consumption above 21 units a week, diabetes mellitus, depression, physical inactivity, smoking, traumatic brain injury, late-life hearing loss, social isolation, and exposure to air pollution(*3*).

In 2019, the World Health Organization (WHO) issued widely-recognized guidelines on risk reduction for cognitive decline and dementia (*30*). The guidelines provide the knowledge base for healthcare providers, governments, policy-makers and other stakeholders to reduce the risks of cognitive decline and dementia.

Knowledge about risk factors is also translated into preventive interventions for individuals at risk (selective prevention) to preserve or improve cognitive function and delay or prevent dementia (*31*). While early intervention studies focused on one factor at a time (single-domain intervention studies), multi-domain interventions focus on several modifiable risk factors simultaneously among those at risk for cognitive decline and dementia. The prototype Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) Study, reported a benefit of a multi-domain lifestyle intervention on cognitive function over two years (*32*). Similar European trials, such as the French Multi-domain Alzheimer Preventive Trial (MAPT) and the Dutch Prevention of Dementia by Intensive Vascular Care (Pre-DIVA) trial have been less conclusive. However, benefits for cognitive function in specific subgroups of adults with higher

risk for dementia were suggested (*33,34*). These promising, but still inconsistent results have led to World-Wide FINGERS (WWFINGERS). WWFINGERS is a global, interdisciplinary network with a mission to share knowledge and experiences on trials for dementia prevention and risk reduction, harmonize data, and plan joint international initiatives for the prevention of cognitive impairment and dementia (https://wwfingers.com/#about). WWFINGERS brings together culturally-specific lifestyle trials from over 40 countries comprised of dietary guidance, physical exercise, cognitive training, social activities and management of vascular and metabolic risk factors. These trials differ by individuals targeted (asymptomatic states to early symptomatic stages of dementia), risk factors addressed, and cultural, geographical, and economic settings (*31*). Another ongoing multi-domain lifestyle trial is German AgeWell.de, a pragmatic, clustered, randomized control trial addressing cognitive decline in a primary care population at increased risk for dementia (*35*).

Although multi-domain interventions seem promising for selected prevention in high-risk individuals, the data are inconclusive. Questions remain, referring to the intervention 'dose' needed to change behaviour, the optimal intervention window during the life course, target groups, best modes of intervention delivery (face-to-face versus virtual), and suitable implementation settings (e.g. primary care) (*36*). AD prevention is a dynamic research field. The potential for dementia prevention is huge, however it is not even close to be fully understood.

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COINFLICTS OF INTEREST

S.T. has served as advisory board member for Roche, Biogen, Grifols, and Eisai. No other potential conflicts of interest relevant to this article exist.

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Table 1: A/T/N Classification

Amyloid (A) and tau (T) are considered as the defining biomarkers of AD. Neurodegeneration (N) is used to stage severity of the disease (independently from AD pathology).

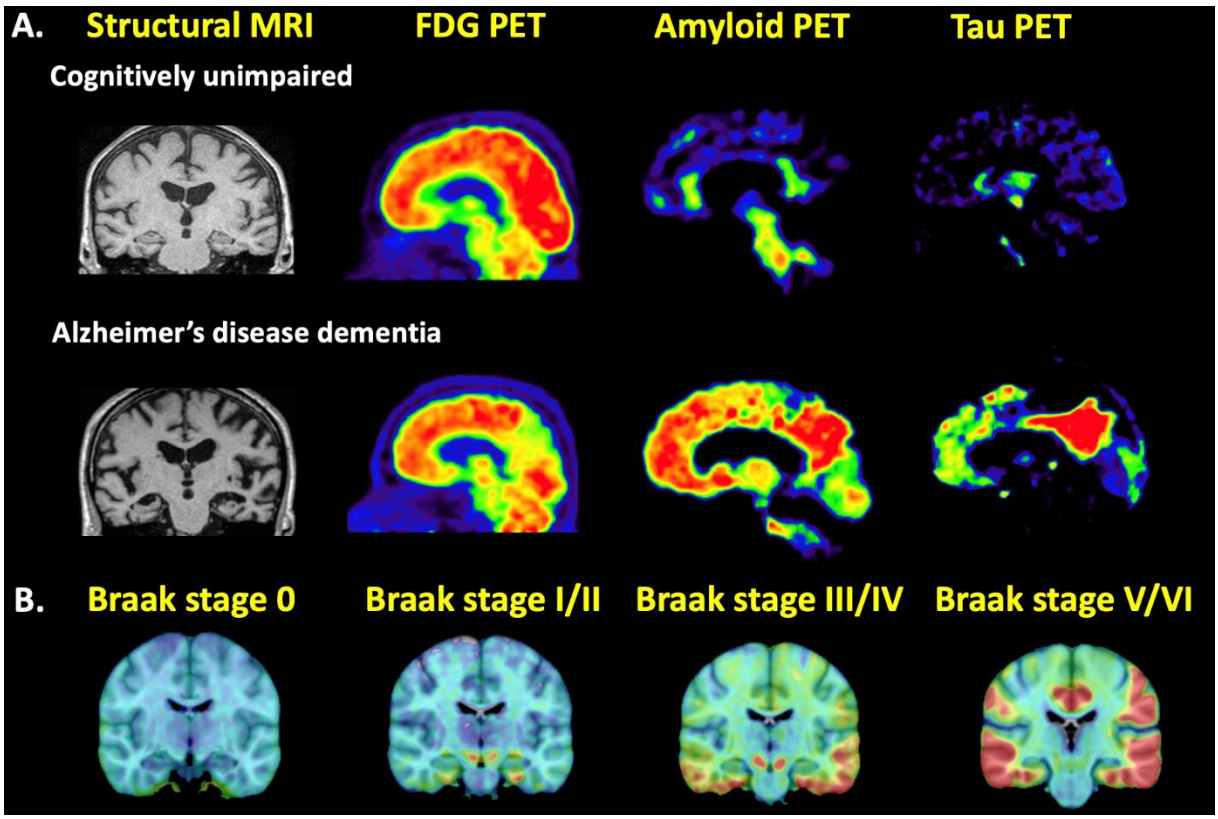
A	Decreased CSF Aβ42, or Aβ42/Aβ40 ratio or positive Amyloid PET
T	Increased CSF phosphorylated tau or positive Tau PET
N	Atrophy in structural MRI or decreased uptake in FDG PET or increased CSF total tau

CSF= cerebrospinal fluid, PET = positron emission tomography, MRI = magnetic resonance imaging, FDG = fluorodeoxyglucose

Table 2: Sensitivity and specificity of CSF- and blood-based biomarkers for AD

	Biomarkers		Sensitivity	Specificity	Reference
CSF	$A\beta_{1–42}$		96.4%	89%	(*37*)
	P-tau	mean value of P-tau	81%	91%	(*37*)
		P-tau181	79%	96%	(*38*)
		P-tau217	91%	91%	(*38*)
	T-tau		81%	91%	(*37*)
	combination of $A\beta_{1–42}$ and T-tau or P-tau		90–95%	90%	(*14*)
Plasma	NfL		an unspecific marker of neurodegeneration, useful for monitoring progression of disease		(*39*)
	Aβ42/Aβ40		70%	70%	(*16*)
	P-tau181		92%	87%	(*17*)
	P-tau217		93%	83%	(*18*)

Figure 1: Imaging features of AD



Panel A shows the different neuroimaging profiles of a cognitively normal individual and a patient with Alzheimer's disease dementia in terms of (from left to right) brain atrophy on T1-weighted MRI, glucose hypometabolism on FDG PET, amyloid burden on PIB PET and tau load on flortaucipir PET. Panel B shows that the neuropathological staging system of neurofibrillary tangles proposed by Braak and Braak can be recapitulated using tau PET using the ligand [^{18}F]RO948 and shows increasing tau PET retention from stage 0 (left) to stage V/VI (right).

Supplementary material

S1. Supplementary Table 1: Key neuropathogenic events in AD

measured by PET neuroimaging

Event	**Tracer**	**In vivo findings**
Amyloid accumulation	^{18}F-Flutemetamol ^{18}F-Florbetaben ^{18}F-Florbetapir ^{11}C-PIB	Higher global levels of amyloid in amyloid-sensitive PET in >50% of cases with mild cognitive impairment (MCI), and in >90% of Alzheimer's disease (AD) dementia cases. Amyloid accumulation on PET replicates the sequence of neocortical and subcortical region involvement suggested from autopsy data. Amyloid PET is a disease defining biomarker in diagnostic research criteria, recognized as surrogate endpoint in a regulatory decision by FDA in June 2021, and can change diagnosis and disease management in clinical care
Tau accumulation	^{18}F-Flortaucipir, ^{18}F-MK6240, ^{18}F-RO948	Accumulation in medial temporal lobe areas corresponding to chronological age and episodic memory performance; spread to neocortical areas may depend on the presence of amyloid.

Synaptic dysfunction	^{18}F-FDG	Consistent pattern of hypometabolism in MCI cases that is predictive for conversion to AD dementia
Neuroinflammation	^{11}C-PK11195 ^{18}F-DPA714	Indication of non-linear effect with decreased binding in prodromal and higher binding in manifest AD. In AD dementia increased uptake in the precuneus, parietal, temporal cortex, and medium and posterior cingulate.
Cholinergic dysfunction Cholinesterase	^{11}C- MP4A ^{11}C-PMP	Cholinesterase activity reduced; findings vary across stages of AD progression with initial increases and later decreases reported.
Nicotinic receptor binding	^{18}F-flubatine	Receptor binding was widely reduced, but upregulation possible in early AD stages. Overall level of evidence is limited.

Supplementary Table 2: Core cognitive symptoms, neuropathology and commonly used diagnostic criteria for AD and relevant differential diagnoses

	Peak age (years)	**Core domains**	**Neuropathological key aspects**	**Diagnostic criteria**
AD	Sporadic 60 + years Familial 30's and 40's years	Typical AD: Episodic memory Atypical AD (examples): ♦ Logopenic variant: impaired spontaneous speech and repetition ♦ Posterior cortical atrophy: impaired visuo-constructive abilities, simultanagnosia, optic ataxia	Extracellular amyloid-ß and intracellular aggregates of hyperphosphorylated tau (neurofibrillary tangles)	National Institute on Aging Alzheimer's Association; International Working Group (IWG-2); Biomarker based NIA-AA research framework (A/T/N)
FTLD	50's and 60's years	Behavioral variant: Executive function / Behavior Primary progressive aphasia:	Intracellular aggregates of hyperphosphorylated tau aggregates, TDP43 (TAR-DNA-binding protein-43)	Behavioral variant, revised criteria Primary progressive aphasia

		♦ Non-fluent variant: agrammatism, apraxia of speech ♦ Semantic variant: naming and single word comprehension	or FUS (fused-in-sarcoma protein)	
PDD	70 + years	Executive function, motor symptoms prior to cognitive impairment	α-Synuclein aggregate in neuronal perikarya and processes (Lewy bodies/neurites)	Movement Disorder Society
LBD	60's and 70's years	Executive and visual spatial function, visual hallucinations and fluctuating attention	α-Synuclein aggregate in neuronal perikarya and processes (Lewy bodies/neurites)	DLB Consortium

AD = Alzheimer's disease, FTLD = frontotemporal lobe degeneration, PDD = Parkinson's disease dementia, LBD = Lewy body dementia

S1. Resting state EEG as a promising approach for AD diagnosis and screening

Complementary to established fluid and neuroimaging biomarkers of AD, eyes-closed resting-state electroencephalographic (rsEEG) allows detecting the effect of AD neuropathology on neurophysiological oscillatory mechanisms underpinning wake-sleep and vigilance regulators. These mechanisms are crucial for patients' quality of life as they determine, for example, the ability to watch a TV program and follow a quiet conversation (*1*). They are grounded on ascending neuromodulating subcortical systems affecting thalamocortical oscillatory circuits that dynamically underpin cortical arousal in the regulation of quiet vigilance. EEG examinations come at the additional advantage to be inexpensive and non-invasive.

In research studies, at the group level, AD patients with dementia or MCI were characterized by abnormally higher delta and theta power density or sources and interrelatedness measures between electrodes/sources in widespread regions. In contrast, posterior alpha power density and interrelatedness were generally poor.

At the individual level, these measures allowed classifications with > 80% accuracy in discriminating between patients with AD dementia or MCI and control individuals, but differential diagnostic value in comparison with non-AD dementias is still unclear. A promising multicentric research model of a North-Baltic Consortium used multiple spectral rsEEG markers and several control groups in step-wise comparisons to test the detection accuracy of AD vs cerebrovascular disease, depression, and Lewy body dementia. It provided a classification accuracy > 80% in computational designs but less accuracy in a daily clinical workup . So rsEEG is experiencing a revival in the diagnostic application for AD, but still is not part of routine diagnosis.

A very attractive new avenue for rsEEG markers is opened by mobile small wireless EEG systems with consumer-grade hardware and dry scalp electrodes, usable at home for periodic rsEEG recording sessions in long-term monitoring trials. Previous studies showed that these systems record rsEEG activity with reasonable duration, quality of signal-to-noise ratio, and reliability. The applications were successful in old seniors at risk of or already experiencing cognitive deficits. In future these systems may allow non-invasive and inexpensive ecologically valid screening of people at risk for AD.

Supplementary Table 3: Approved antidementia drugs

Drug	Form of administration	Side effects	Starting dose	Maximal dose
Mild to moderate AD dementia				
Donepezil (Cholinesterase inhibitor)	Tablet	nausea diarrhea vomiting muscle cramps bradycardia	5 mg evening	10 mg
	Melting tablet		5 mg evening	10 mg
Galantamine (Cholinesterase inhibitor)	Retarded capsule	nausea diarrhea vomiting muscle cramps bradycardia	8 mg morning	24 mg
	solution (1 ml = 4 mg)		4 mg b.i.d. (morning and evening)	24 mg
Rivastigmine (Cholinesterase inhibitor)	Hard capsule	nausea diarrhea vomiting muscle cramps bradycardia	1,5 mg b.i.d. (morning and evening)	12 mg
	solution (1 ml = 2 mg)		2 mg b.i.d. (morning and evening)	12 mg
	transdermal (patch)		4.6 mg/24 h	13.3 mg/24 h*

Drug	Form of administration	Side effects	Starting dose	Maximal dose
Moderate to severe AD dementia				
Memantine (partial glutamate antagonist)	tablet	agitation dizziness confusion. constipation hypertension	5 mg morning	20 mg
	Drops/gtt (20 gtt = 10 mg)		5 mg morning	20 mg
Mild to moderate Parkinson's disease dementia				
Rivastigmine (Cholinesterase inhibitor)	Hard capsule	nausea diarrhea vomiting muscle cramps bradycardia	1.5 mg b.i.d. (morning and evening)	12 mg
	* The maximum dosage of the rivastigmine transdermal patch is 9.5 mg/24 h. With further worsening of symptoms within six months, a dosage of 13.3 mg/24 h is possible.			

S2. Non-pharmacological treatments

There is a wide range of non-pharmacological treatments (NPT) for AD, however few have undergone standardized scientific evaluation. Consequently, evidence for the effectiveness of many NPT remains scarce or unconvincing. The majority of published NPT studies included cognitive healthy older people or did not include a control group.

One key element of NPT are cognitive interventions. A recent meta-analysis (*2*) included 36 trials with patients with MCI or dementia. There was an overall positive effect on global cognition with cognitive interventions compared to controls. However, the methodological quality of the reviews included was low or critically low. Cognitive interventions are often classified into cognitive stimulation (offering a range of different cognitive and social tasks), cognitive training (standardized training of specific cognitive domains) and cognitive rehabilitation (individualized targets and use of restoration and/or compensatory strategies). The National Institute for Health and Care Excellence (NICE) deems only cognitive stimulation to be sufficiently evaluated with a positive effect on cognition. Therefore, it is the only NPT explicitly recommended in NICE guidelines for people living with mild to moderate dementia. Not every statistically significant change in global cognition is meaningful from a clinical perspective. A review on cognitive interventions, found that cognitive stimulation (versus non-active and active controls) positively affected global cognition (*3*). However, only 64% of cognitive stimulation trials reported a clinically-relevant change in Mini-Mental Status Examination (MMSE) score.

Cognitive interventions target key symptoms of patients with AD and are considered low risk for the patient. Studies indicate the potential benefit of cognitive interventions. However, NPT involving physical activity, diet, and reminiscence therapy often lack rigorous evidence, clinically-significant endpoints, and/or standardization of a single or combination NPT. NPT have potential,

however whether NPT that are beneficial for brain health in older cognitively unimpaired persons are also effective for people with MCI, AD or other types of dementia is unknown. The importance of dyadic treatments has also gained attention to address the impact of dementia on entire families rather than the affected person alone. A dyadic perspective of dementia treatment includes support and/or training for nonprofessional caregivers. Family caregivers' own physical and mental health needs should be assessed and, if needed, additional interventions offered. Individualized computer-based expert systems are helpful to identify unmet caregiver needs. In addition, evidence shows that multicomponent interventions like the REACH II program (REACH - Resources for Enhancing Alzheimer's Caregiver Health initiatives) reduces depressive symptoms in caregivers and can be delivered by community agencies. Several dyad interventions have shown to be effective for both caregiver and patient, however, widespread dissemination and robust evidence are lacking.

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