Supplemental 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.

Supplemental 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.

Supplemental 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.

References

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