

Pharmacoeconomics: studies to date and methodological issues

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and other instruments
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clinical efficacy studies?
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Effectiveness studies and
naturalistic designs
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Review of pharmacoeconomic data from previous clinical trials

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Montreal, Canada

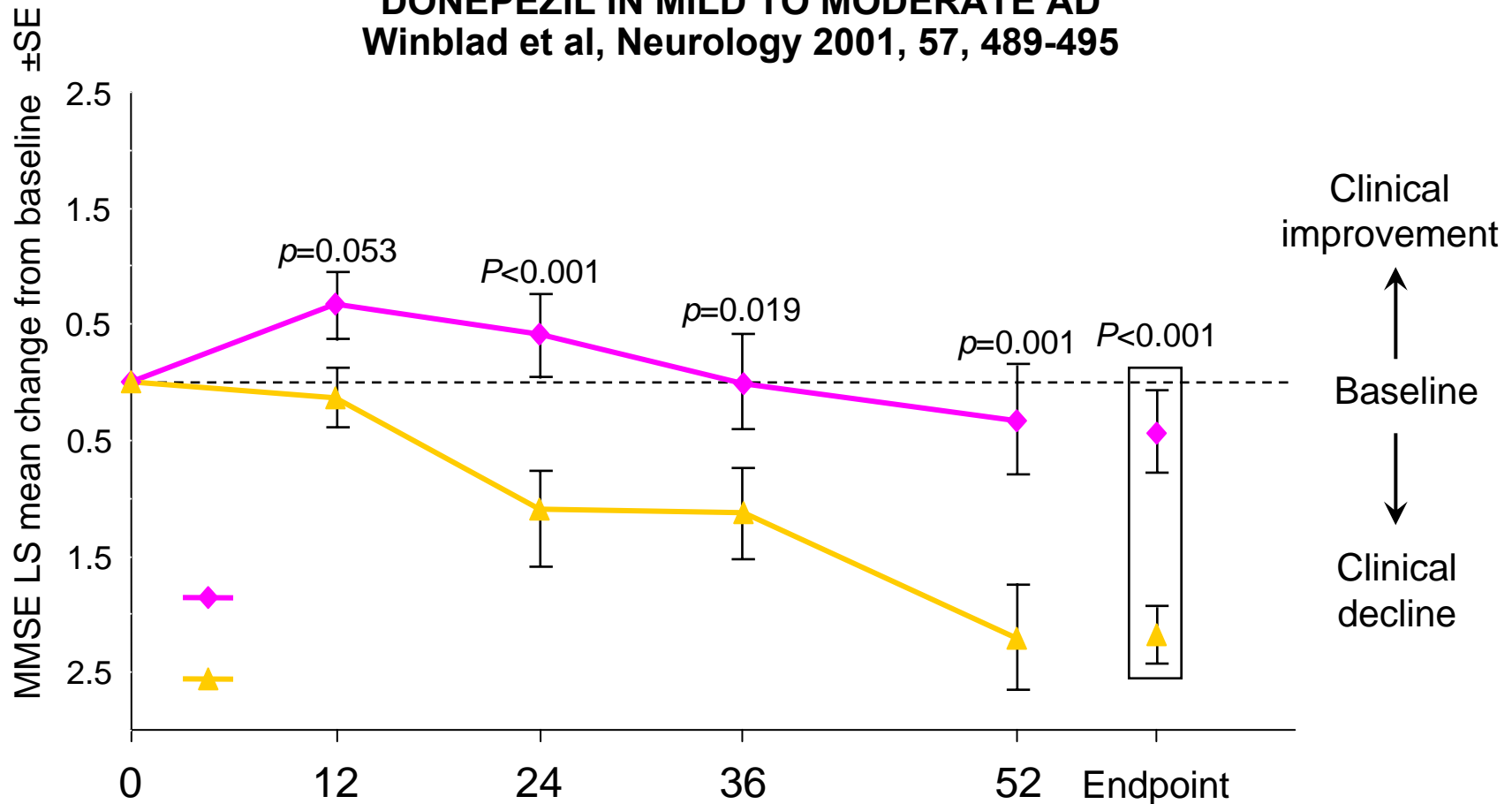
Overview of four RCT with prospective pharmacoeconomic data

Study	Drug vs placebo	Duration (weeks)	MMSE
Nordic	Donepezil	52	10-26
MSAD	Donepezil	24	5-17
AD2000	Donepezil	108	10-26
Memantine monotherapy/US	Memantine	28	3-14

Clinical efficacy outcomes/publications

Study	Clinical efficacy outcomes (* = significant at endpoint)	References
Nordic	<u>GBS</u> , MMSE*, PDS*, NPI, GDS*	Winblad et al Neurology 2001;57:489-495
MSAD		
AD2000		
Memantine monotherapy/USA		

DONEPEZIL IN MILD TO MODERATE AD
Winblad et al, Neurology 2001, 57, 489-495



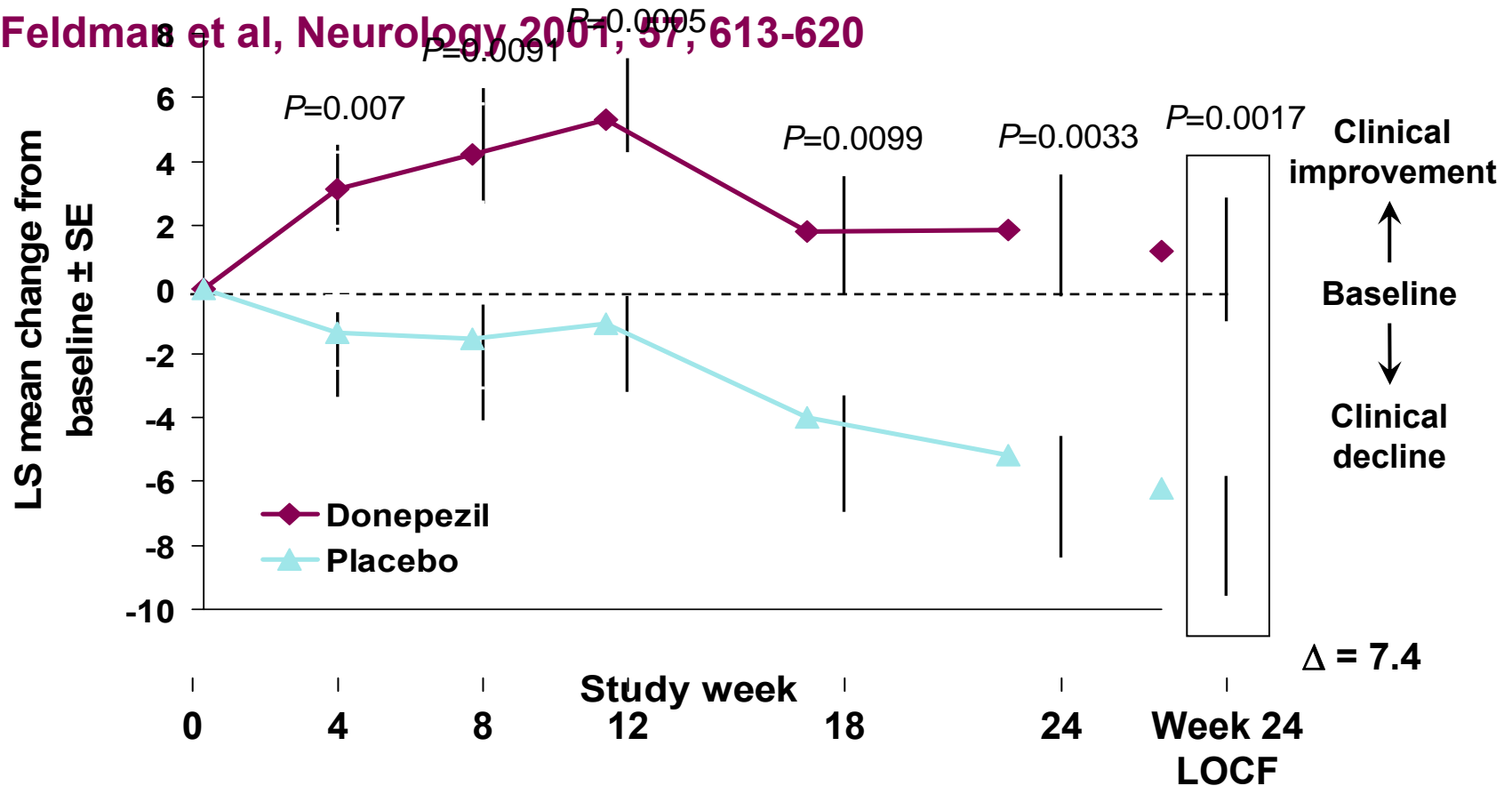
donepezil	<i>n</i> = 135	127	121	104	91	(135)
placebo	<i>n</i> = 137	128	120	105	98	(137)

Clinical efficacy outcomes/publications

Study	Clinical efficacy outcomes (* = significant at endpoint)	References
Nordic	<u>GBS</u> , MMSE*, PDS*, NPI, GDS*	Winblad et al Neurology 2001;57:489-495
MSAD	<u>CIBIC+</u> *, sMMSE*, SIB*, DAD*, IADL*, PSMS*, NPI*, FRS*	Feldman et al, Neurology 2001;57:613-620
AD2000		
Memantine monotherapy/USA		

COGNITIVE EFFECTS OF DONEPEZIL IN COMMUNITY MODERATE/SEVERE AD

Feldman et al, Neurology 2001, 57, 613-620



Donepezil	n= 71	67	61	66	63	62	(71)
Placebo	n= 73	70	61	62	65	63	(73)

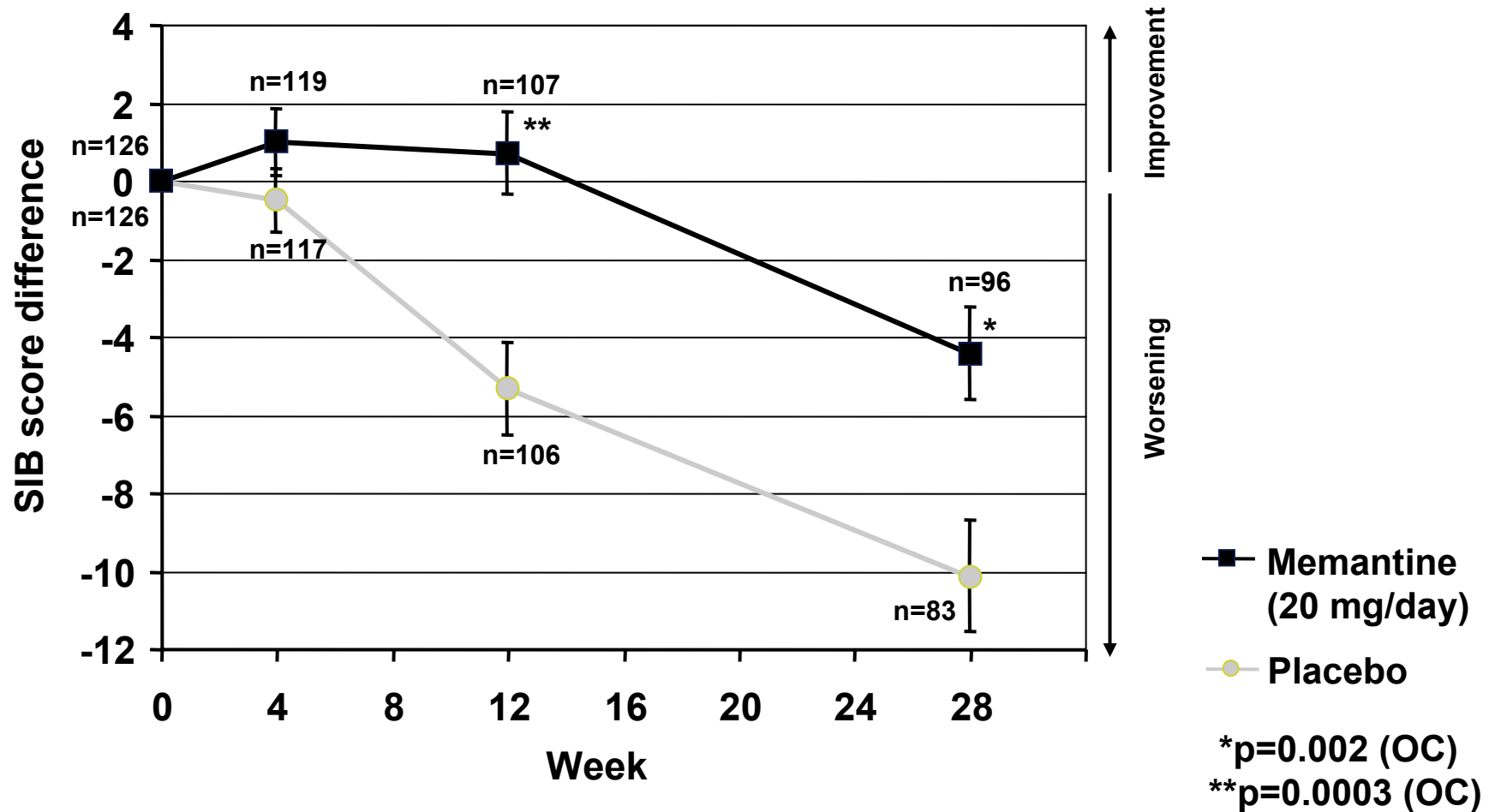
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AD2000	<u>Entry to institutional care, loss of 2/4 or 6/11 BADLS</u> , BADLS*, NPI, MMSE*, GHQ-30, death from AD, compliance	AD2000 Lancet 2004;363;2105-15
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Memantine monotherapy/USA	<u>CIBIC+</u> , <u>ADCS-ADL</u> *, SIB*, MMSE, GDS, FAST*, NPI	Reisberg et al, NEJM 2003;348:1333-141

COGNITIVE EFFECTS OF MEMANTINE



Health economics outcomes/publications

Study	Health economics outcomes (* = significant at endpoint)	References
Nordic	RUD	Wimo et al, DGCD 2003;15: 44-54
MSAD	CAUST	Feldman et al Neurology 2004; 63: 644-650
AD2000	CAS	AD2000 Lancet 2004;363;2105-15
Memantine monotherapy/USA	RUD	Wimo et al, Pharmacoeconomics 2003; 21:1-14

Nordic Family Impact Study (Wimo et al)

US\$ 2006 per year	donepezil	placebo	difference
Donepezil cost	1538	0	1538
Patient direct costs	18211	19399	-1188
Caregiver direct costs	815	1241	-427
Informal care costs	9435	10676	-1241
Total costs	29998	31316	-1318

MSAD study (Feldman et al)

US\$ 2006 per 24 weeks	donepezil	placebo	difference
Donepezil cost	701	0	701
Patient direct costs	3026	3500	-474
Caregiver direct costs	139	113	26
Informal care costs	4551	4746	-195
Total costs	8418	8356	62
Adjusted total costs	8248	8524	-276

AD2000 (AD2000 group)

US\$ 2006 per 60 weeks	donepezil	placebo	difference
Donepezil cost	Not included	-	
Patient direct costs (institutionalisation not included)	5141	4240	901
Caregiver direct costs	Not reported	Not reported	Not reported
Informal care costs	Not reported	Not reported	Not reported (0.6 hours less per day in donepezil group)
Total costs	5141	4240	901

Memantine study (Wimo et al)

US\$ 2006 per month	memantine	placebo	difference
Patient direct medical costs	281 (memantine 173)	89	192
Direct non-medical costs	94	636	-542
Informal care & caregiver costs	8332	8687	-356
Total costs	8707	9413	-706
Adjusted total costs	8535	9844	-1310

Conclusions

- In four RCT with prospectively defined pharmaco-economic evaluations of costs between active drug (donepezil or memantine) vs placebo, three showed lower costs associated with active drug treatment, and one no significant increase in costs.
 - These studies were of 24 to 102 weeks duration, and included patients in mild to severe stage of AD (MMSE 3-26) living in the community.
 - $\frac{3}{4}$ studies were not powered to establish pharmaco-economic benefit and $\frac{1}{4}$ was underpowered overall.
 - Pivotal studies should include a prospectively defined pharmaco-economic component as supportive evidence for the cost-effectiveness of the demonstrated clinical benefits.
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Discussion points

- Are there other designs that may show more convincingly cost-savings associated with clinical benefit? For example, preservation of function survival using donepezil vs placebo over 54 weeks (Mohs et al, Neurology 2001; 57: 481-488).
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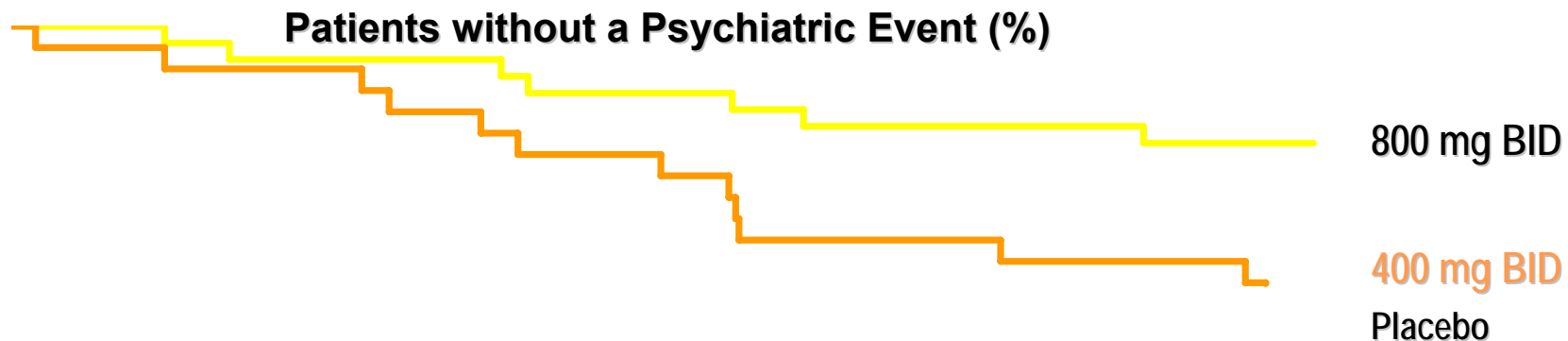
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 - Would delay of progression to a disease milestone be more convincing to clinicians and payers?
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TARENFLURBIL PHASE II TIME TO PSYCHIATRIC EVENT

(Mild Patients, MMSE ≥ 20)



Karolinska
Institutet



	# of Patients with AE	p value	Median Time to Event	p value
Placebo	18	0.020	106 days	0.011
800 mg BID	7		>333 days	

Days on Study

Discussion points

- Are there other designs that may show more convincingly cost-savings associated with clinical benefit? For example, preservation of function survival using donepezil vs placebo over 54 weeks (Mohs et al, Neurology 2001; 57: 481-488).
 - Would delay of progression to the next disease milestone be more convincing to clinicians and payers?
 - The four RCT with prospective pharmacoeconomic data were done at a time when placebo could be used in mild to severe AD up to 12 months. Should we move to a pre-dementia stage of AD without CI and memantine?
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W Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS-ADRDA criteria

Bruno Dubois*, Howard H Feldman*, Claudia Jacova, Steven T DeKosky, Pascale Barberger-Gateau, Jeffrey Cummings, André Delacourte, Douglas Galasko, Serge Gauthier, Gregory Jicha, Kenichi Meguro, John O’Brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Yaakov Stern, Pieter J Visser, Philip Scheltens

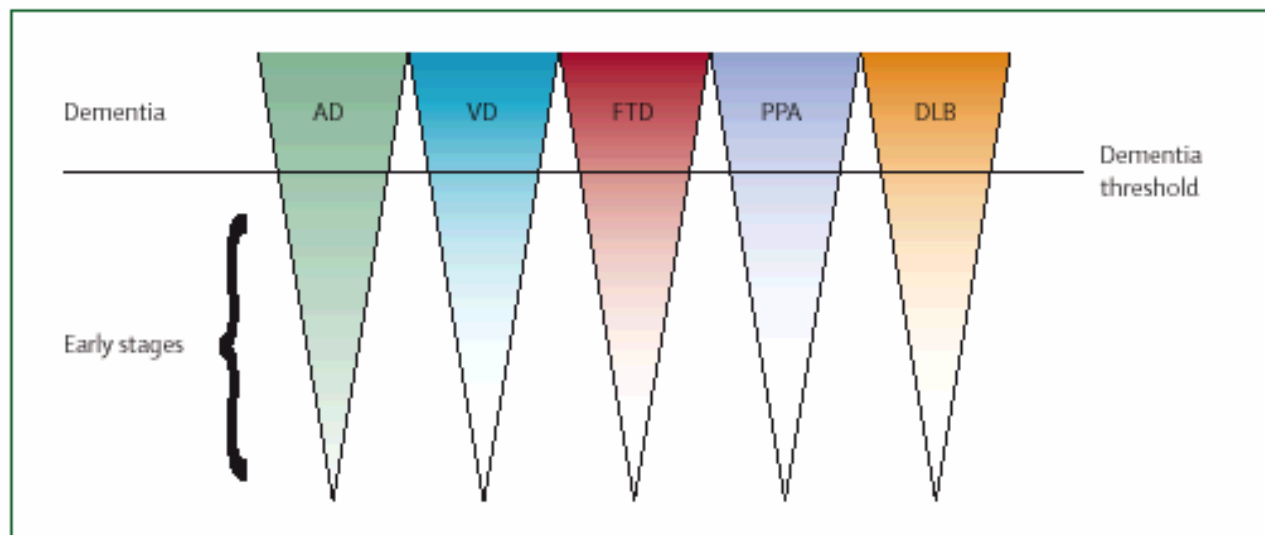


Figure: Alzheimer’s disease starts and should be identified before the occurrence of full-blown dementia (as for other dementing conditions)

AD=Alzheimer’s disease; VD=vascular dementia; FTD=frontotemporal dementia; PPA=primary progressive aphasia; DLB=dementia with Lewy bodies.



Panel 2: Diagnostic criteria for AD

Probable AD: A plus one or more supportive features B, C, D, or E

Core diagnostic criteria

A. Presence of an early and significant episodic memory impairment that includes the following features:

1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled
3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances



Supportive features

B. Presence of medial temporal lobe atrophy

- Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)

C. Abnormal cerebrospinal fluid biomarker

- Low amyloid β_{1-42} concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
- Other well validated markers to be discovered in the future

D. Specific pattern on functional neuroimaging with PET

- Reduced glucose metabolism in bilateral temporal parietal regions
- Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP

E. Proven AD autosomal dominant mutation within the immediate family

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