Review of MCI Clinical Trials

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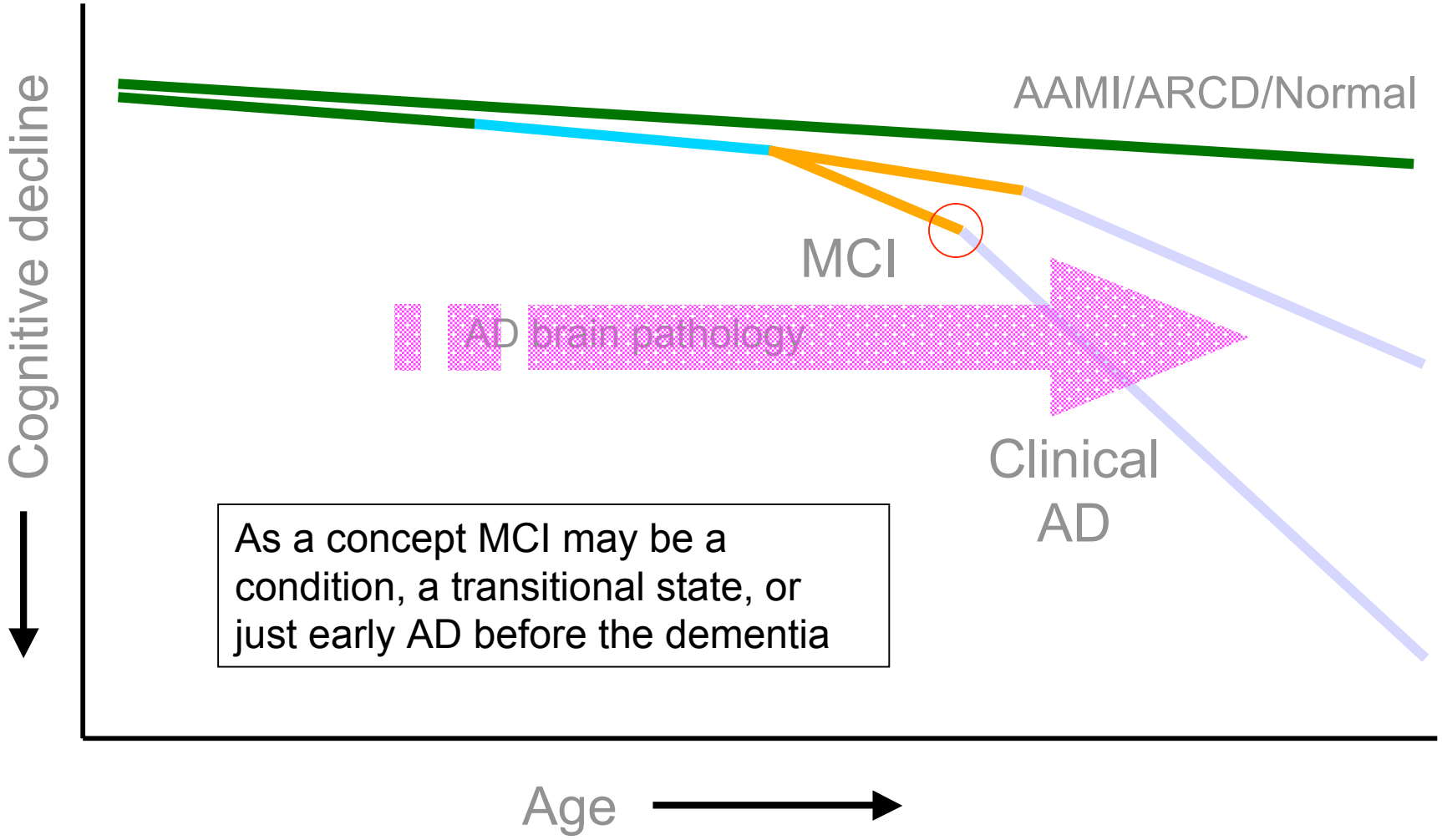
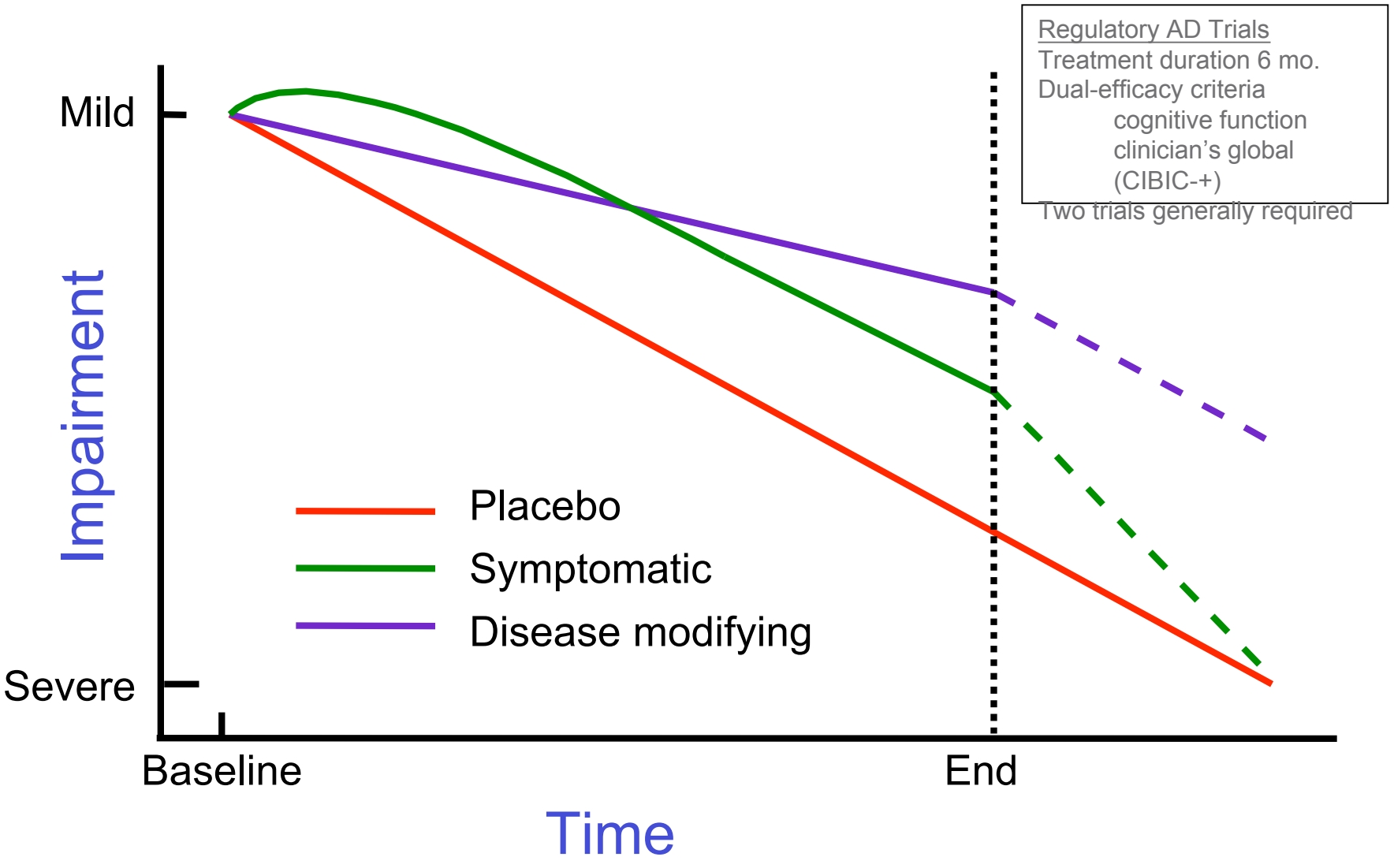
- Forest Laboratories Inc.
- Johnson & Johnson (Janssen)
- Lundbeck and Merz
- Novartis
- Pfizer
- UCB

Course of Aging, MCI and AD



Symptomatic effects *vs.* slowing disease progression: current regulatory status



The MCI *Trials Imperative*

- Desire for early diagnosis of AD
  - Dissatisfaction with AD criteria
- Desire to prevent illness
  - MCI trials as proxies for prevention trials?
  - Back door prevention trials to save sample sizes and duration
- Development of drug candidates, and new therapeutic targets
  - Implying that earlier intervention is better
- Pharma's desire for expanded labeling
  - "Disease modification"
- *Perceived* ethical quandaries of placebo controls in AD
- Huge potential therapeutic impact

- Main caveats:
  - MCI is an unstable and moving target
  - MCI trials are informed by interesting observational studies, the findings of which may not apply to clinical trials
  - The main outcomes: time to diagnosis of AD *or* rate of cognitive decline are confounded by 'symptomatic' effects

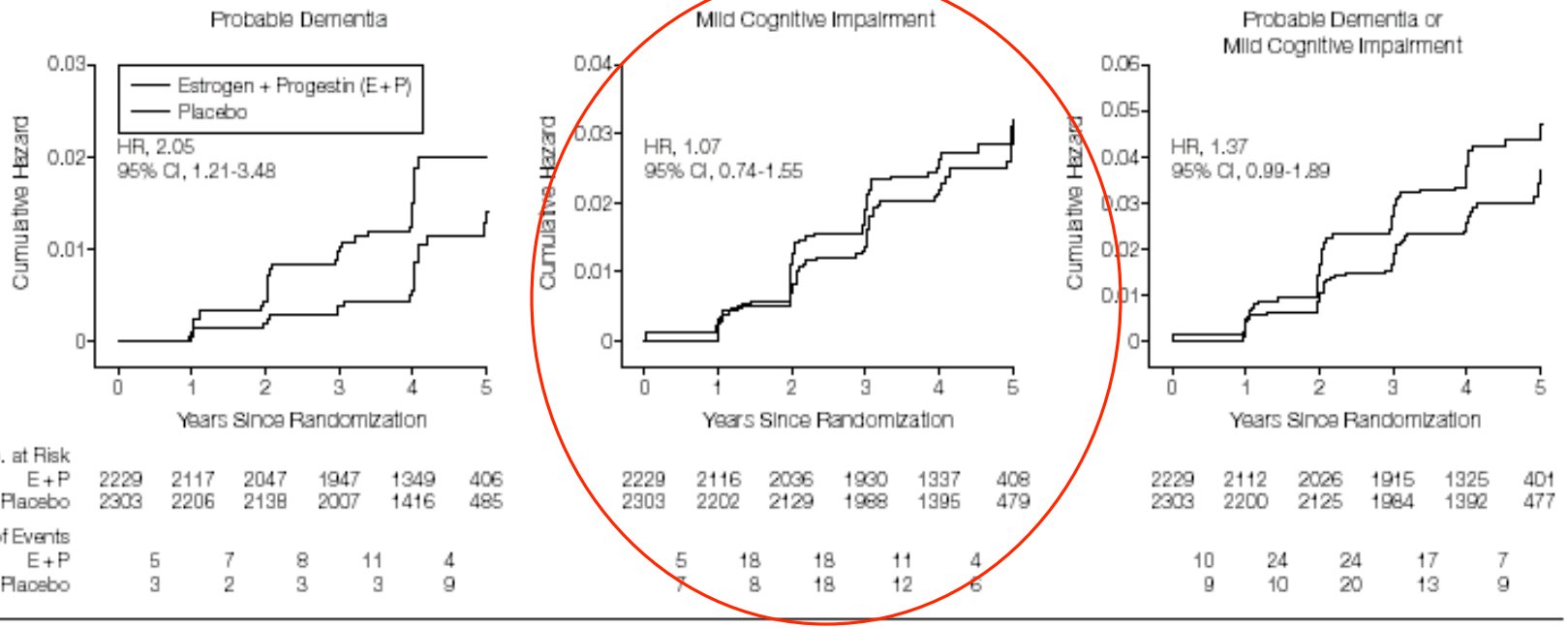
Women's Health Initiative Memory Study: CEE/progestin arm (JAMA 2002)

Table 2. Cases of Probable Dementia and Mild Cognitive Impairment: Frequencies and Rates for 10 000 Person-Years

Outcome	Estrogen + Progestin (n = 2229)	Placebo (n = 2303)	HR (95% CI)
Probable dementia, No.	40	21	
Follow-up, mean (SD), y	4.01 (1.21)	4.06 (1.18)	
Rate per 10 000 person-years	45	22	2.05 (1.21-3.48)
Mild cognitive impairment, No.	56	55	
Follow-up, mean (SD), y	3.99 (1.23)	4.04 (1.20)	
Rate per 10 000 person-years	63	59	1.07 (0.74-1.55)
Probable dementia or mild cognitive impairment, No.	85	66	
Follow-up, mean (SD), y	3.97 (1.24)	4.03 (1.21)	
Rate per 10 000 person-years	95	71	1.37 (0.99-1.89)

Abbreviations: CI, confidence interval; HR, hazard ratio.

Figure 2. Cumulative Hazards Ratios for a Diagnosis of Probable Dementia and Mild Cognitive Impairment



CI indicates confidence interval; HR, hazard ratio. Data shown only through 5 years of follow-up because numbers at risk are too small after this point for precise

A Few MCI observational studies: conversion to AD

Author	Year	Location	Criteria	Yrs Fol.	Conversion rate/yr
Flicker	1991	NY	GDS 3	2	25
Tierney	1996	Toronto	Mem imp	2	12
Bowen	1997	Seattle	Isolated mem	4	12
Devanand	1997	NYC	? Dementia	3	15
Geerlings	1999	Amsterdam	Mem imp	3	12
Petersen	2001	Roch MN	MCI	4	12
Daly	2000	Boston	CDR 0.5	3	6
Bennett	2002	MO (nuns)	MCI	4.5	8
Larrieu	2002	France	MCI	5	8

Predictors: APOE4, memory, hippocampal volume

ADAS-Cog Does Not Distinguish MCI and AD

Table 3. ADAS-Cog Scores by Participant Groups*

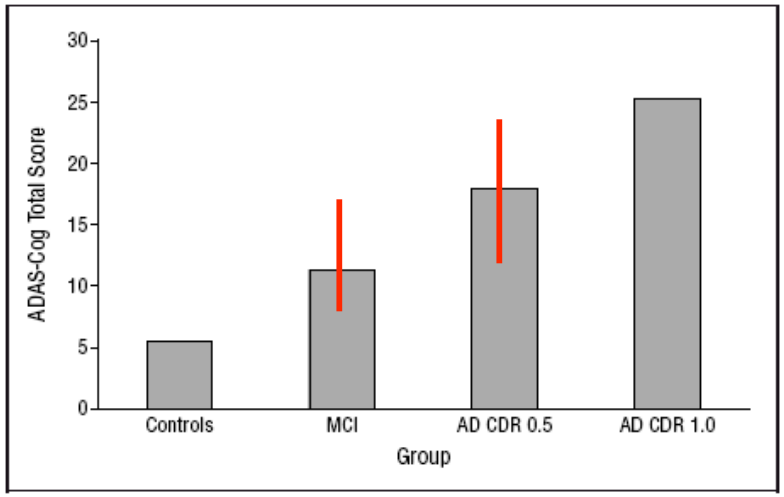
Variable	Controls (n = 107), Score, Mean ± SD	MCI Group (n = 769) Score, Mean ± SD	MCI Group (n = 769) z Score	AD (CDR 0.5) Group (n = 122) Score, Mean ± SD	AD (CDR 0.5) Group (n = 122) z Score	AD (CDR 1.0) Group (n = 183) Score, Mean ± SD	AD (CDR 1.0) Group (n = 183) z Score	P Value	P<.05†
ADAS-Cog total	5.6 ± 3.3	11.3 ± 4.4	1.7	18.0 ± 6.2	3.7	25.2 ± 8.8	5.9	<.001	a,b,c,d,e,f
ADAS word list immediate recall	2.7 ± 1.2	4.9 ± 1.4	1.8	6.0 ± 1.3	2.8	6.9 ± 1.4	3.6	<.001	a,b,c,d,e,f
ADAS word list recognition	2.0 ± 2.2	4.3 ± 2.8	1.1	6.2 ± 3.1	2.0	7.7 ± 3.0	2.6	<.001	a,b,c,d,e,f
ADAS-Cog without word list items	0.9 ± 1.2	2.1 ± 1.8	1.0	5.7 ± 3.5	4.1	10.7 ± 6.5	8.2	<.001	a,b,c,d,e,f
ADAS word list delayed recall‡	2.6 ± 1.7	6.3 ± 2.2	2.1	8.3 ± 1.7	3.3	8.9 ± 1.5	3.7	<.001	a,b,c,d,e
ADAS score from word list/non–word list items, %	84/16	81/19		68/32		58/42		<.001	b,c,d,e,f

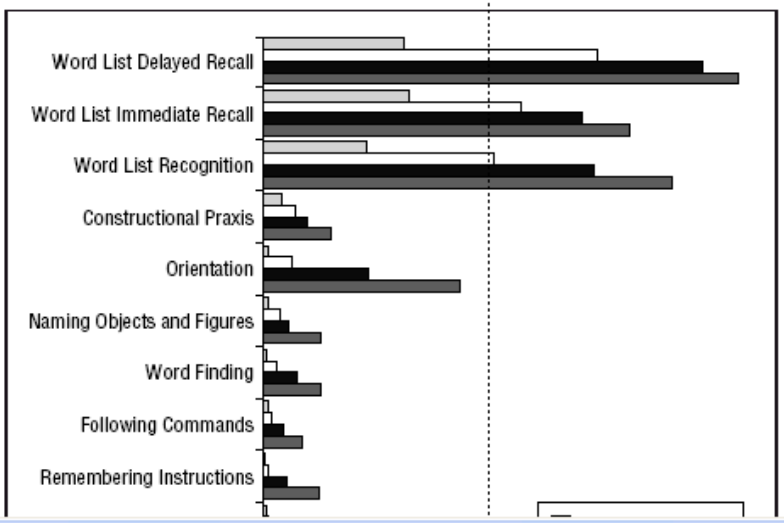
Abbreviations: AD, Alzheimer disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; CDR, Clinical Dementia Rating; MCI, mild cognitive impairment.

*Higher ADAS-Cog total scores and subscores indicate a greater number of errors.

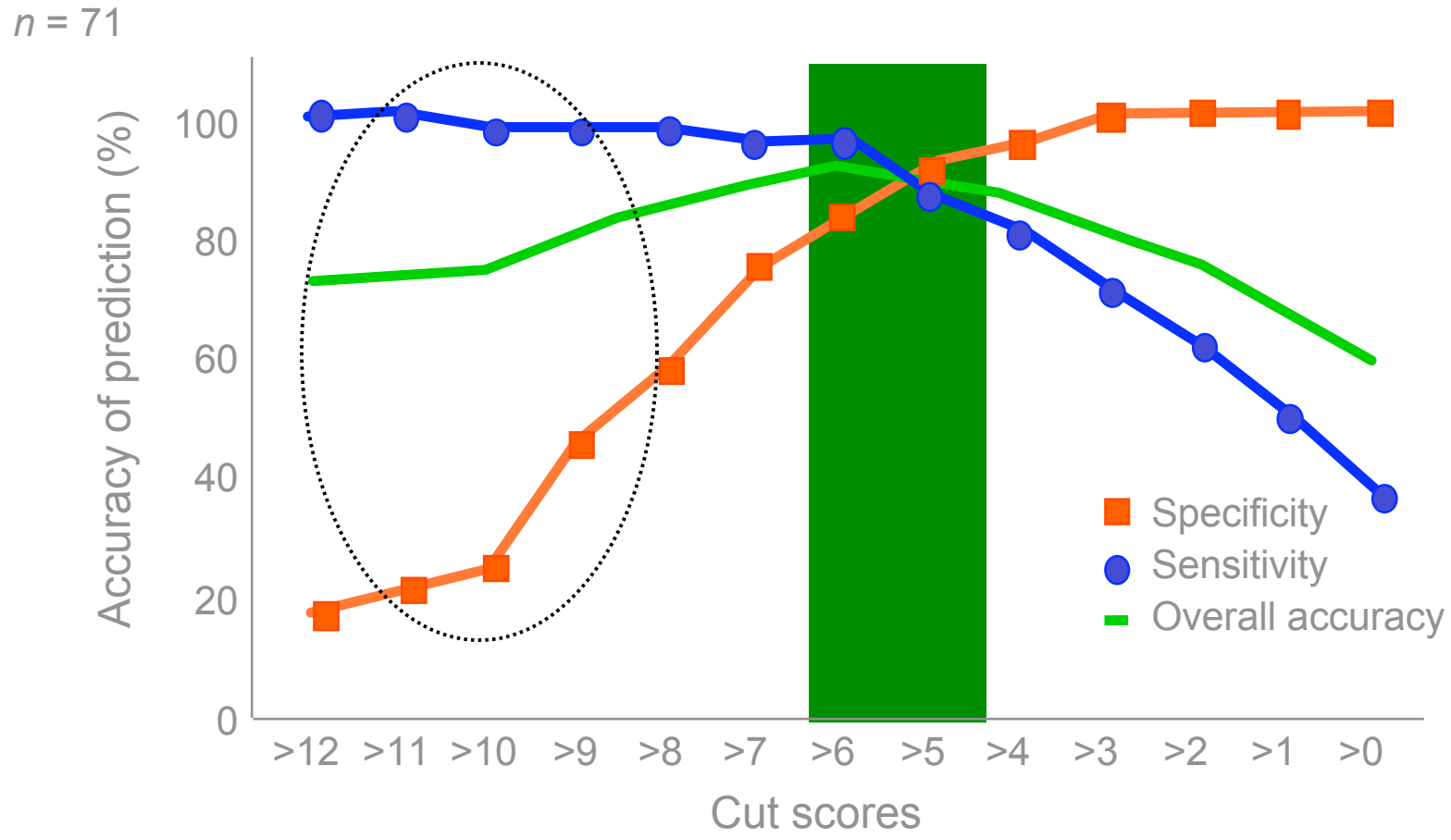
†Indicates significance at $P<.05$ after Bonferroni adjustment for multiple comparisons: a, MCI to control comparison; b, MCI to AD (CDR 0.5) comparison; c, MCI to AD (CDR 1.0) comparison; d, control to AD (CDR 0.5) comparison; e, control to AD (CDR 1.0) comparison; f, AD (CDR 0.5) to AD (CDR 1.0) comparison.

‡ADAS word list delayed recall is not included in the classic 70-point ADAS-Cog total score.



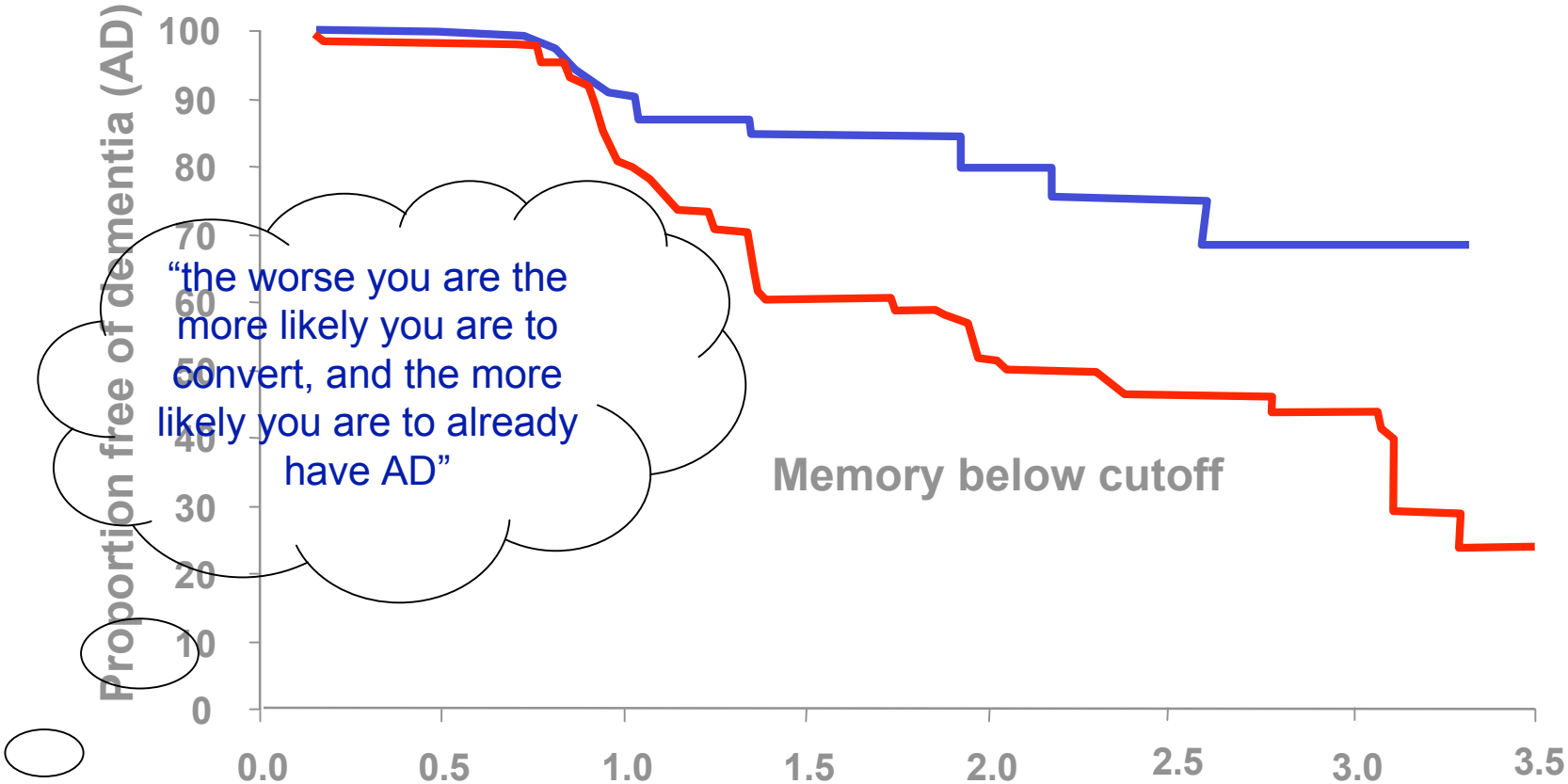


Predicting decline from MCI to AD with NYU delayed paragraph recall



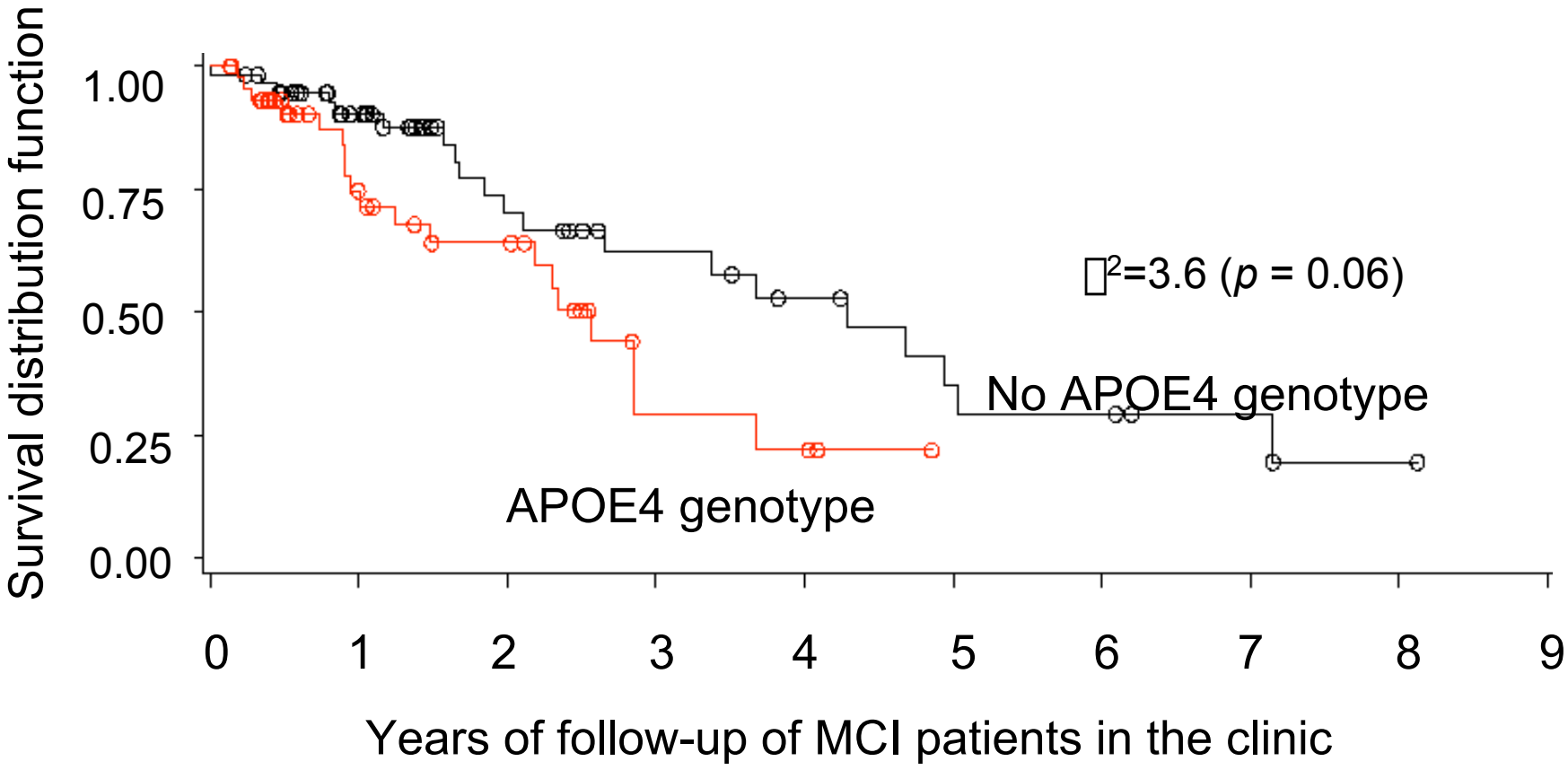
Kluger A *et al.* J Geriatr Psychiatry Neurol 1999; 12: 168–79

Gaming conversion with MCI memory criteria



*Grundman-ADCS pooled data:
WMS-II Logical Memory cutoff scores

APOE4 Predicts Conversion to Dementia



Duara R, et al 2001

Summary: Predictors of Conversion

- Cognition
- APOE 4
- Hippocampal volume
- Depression symptoms
- (Age)

The MCI Trials

MCI Trials – Current Status Rests on Trials Results

- Rofecoxib (Merck): 3, then 4 yr, N = 1457
  - (low) conversion to AD, ADAS cog, SRT, CDR, Blessed
- Donepezil or vitamin E (ADCS/Pfizer): 3 yr, N = 769
  - conversion to AD and ADAS cog
- **Donepezil (Pfizer): 6 mo, N = 269**
  - **ADCS-CGIC (MCI version), mADAScog, symptom change**
- Rivastigmine (Novartis): 3, then 4 yr, N = 1018 (originally 750)
  - (low) conversion to AD, composite neuro-cognitive change
- Piracetam (UCB): 1 yr N = 675
  - symptom progression, rate of decline
- Galantamine (INT-11) (Janssen): 2 yr, N = 898
  - symptom progression, M-ADAS cog, DSST, CDR
- Galantamine (INT-18) (Janssen): 2 yr, N = 1019
  - symptom progression M-ADAS cog, DSST, CDR and MRI
- CX 516, AMPA modulator (Cortex, Servier): 1 mo., N=168
  - Symptomatic

MCI Trials: Inclusion Criteria

Trial Sponsor	MCI Criteria	Cognitive Criteria
ADCS	Age > 54, memory complaints, MMSE > 23, CDR = 0.5 (memory = 0.5 or 1.0), diagnosis of AD cannot be made, HAM-D < 13	WMS-LM II (delayed paragraph recall) < 9 (for 16 yrs education), < 5 (for 8-15 yrs), < 3 (for 0-7 yrs)
Pfizer	Documented memory complaint, MMSE ≥24, CDR = 0.5, (memory score = 0.5 or 1.0), ADL normal or only slightly impaired (maximum score of 1.5 on 3 CDR-ADL items), diagnosis of probable or possible AD cannot be made	WMS-R delayed paragraph recall (≤ 8 for ≥16 years of education, ≤4 for 8–15 years of education, ≤2 for 0–7 years of education
Merck	Age > 64, subject reports memory problem, or informant reports that subject has memory problem, informant reports that memory has declined in past year, MMSE ≥ 24, CDR = 0.5 (memory ≥ 0.5), Blessed ADL total ≤ 3.5, with no part 1 score < 0.5	Rey Auditory Verbal Learning Test ≤ 37
Novartis	Age > 54, CDR = 0.5, 17-item HAM-D < 13	NYU delayed paragraph recall < 9
Janssen	Age > 49, gradual onset, slow progression of clinical decline in cognitive ability consistent with MCI, CDR = 0.5 (and memory score at least 0.5), insufficient impairment of ADLs for diagnosis of dementia	NYU delayed paragraph recall < 11
UCB		
Cortex/ Servier		

Outcome measures for MCI trials

- Conversion to AD (survival design)
  - conversion to CDR = 1.0
  - Adjudication committee
- AD domains
  - cognitive function (modified ADAS cog, other cognitive outcomes)
  - global status or change
  - ADLs
  - behavior
  - quality of life
- Surrogate markers
  - MRI metrics
    - whole brain or hippocampal volume
  - biomarkers
  - pharmocoeconomics

Donepezil MCI 6 Month Trial

- N = 269
- Primary outcomes: CGIC and modified ADASc
- Both not significant
- Other cognitive measures significant

Rofecoxib for MCI

- Expected annual conversion to AD: 10-15%
- N = 1457
  - (MMSE = 24-26, N = 405)
- Rofecoxib, 25 mg/d
- Followed for 3 years, then up to 4 years!
- Conversions, N = 189 (13%)
- 45% dropped out, 40% completed and complied!
- Conversions:
  - Rofecoxib 6.4% / y
  - Placebo 4.5% / y
  - Hazard Ratio 1.46, 95% CI: [1.09, 1.94], p=0.01
- Secondaries: no differences on ADASc, MMSE, SRT, CDR (p = 0.06 favoring placebo), Blessed DRS

Visser et al 2003

Galantamine -11 Outcomes

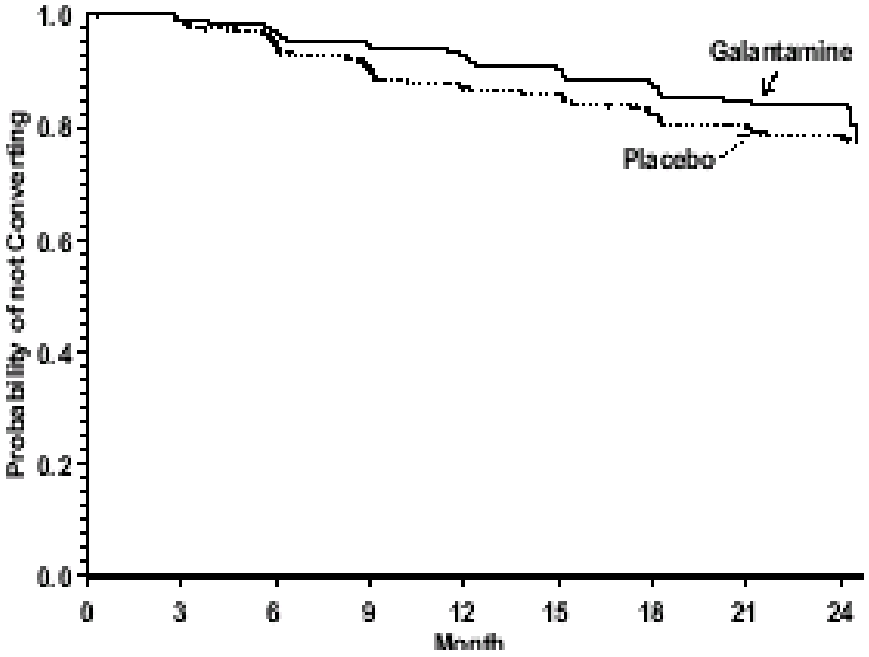
- Gal -11
  - 780 planned, 995 randomized, 898 assessed for efficacy
  - completed Nov 2003
- Dose: 8 – 12 b.i.d.
- Outcomes:
  - Improved cognition at 12 months: mADASc and CDRsb
    - Also CDR, DSST, ADCS-ADLs
  - Delay conversion to dementia at 24 months
- ADASc at month 12 and 24, were -0.6 (5.55) and -1.2 (6.08), galantamine vs. -0.3 (5.22) and -0.7 (6.17) for placebo (p=0.23 and 0.17)
- No significance in conversion to dementia by Month 24 (p=0.146).
- Superior to placebo on CDR-SB scores at Months 12 and 24 (LOCF). Changes were 0.1 (1.06) and 0.3 (1.29) in the galantamine group compared with 0.3 (1.28) and 0.4 (1.45) in placebo at months 12 (p=0.024) and 24 (p=0.028)
- Statistically superior compared with placebo in improving attention, the DSST at Month 12 (LOCF). At Months 12 and 24, the changes from baseline were 2.3 (12.76) and 2.0 (13.71) in galantamine compared with 0.6 (14.05) and 1.0 (15.47) in placebo (p=0.009 and 0.079).
- No differences for: ADCS-ADL/MCI
- Maybe more effective with longer length of illness, greater cognitive severity, with FH of AD

Galantamine -18 Outcomes

- 780 subjects planned, 1062 randomized, 1019 analyzed for efficacy,1058 for safety
- No difference on ADAS-cog/MCI at months 12 and 24 (LOCF)
  - Mean changes (SD) were -0.4 (5.87) and -0.6 (6.54) for galantamine compared with -0.5 (6.05) and -0.7 (6.85) at months 12 and 24
- Not different on conversion to dementia (p=0.619).
- Not different in maintaining CDR-SB at months 12 and 24 (LOCF), 0.3 (1.29) and 0.4 (1.40) for galantamine and 0.3 (1.26) and 0.6 (1.48) for placebo at months 12 and 24,
- Superior on attention DSST at month 24 (p=0.02) but not at month 12 (LOCF)
- No differences for ADLs, ADAS-cog/11, and /13 at months 12 or 24.
- Superior at month 24 in CDR-SB scores (p=0.013).
- In the subgroup with a NYU Delayed Recall of 4-5 superior to placebo with regard to conversion to dementia by month 24 (9% v. 26%; p=0.017)
- In subgroup with delayed to Immediate Recall ratio of >1.0-1.5, approached significance in conversion to dementia (10% v. 16%; p=0.058); 12% of placebo subjects converted by month 24 vs. 4% of galantamine

Galantamine -11 and -18 Outcomes: Conversions from CDR = 0.5 to1.0

- N = 898
- Conversion (gal vs. plc)
  - 1 yr, 6.6% vs. 11.5%
  - 2 yr, 13.3% vs. 18.4%
  - RR = 0.78 (0.6 to 1.1)
- Dropouts
  - 152 vs. 112



- N = 1019
- Conversion (gal vs. plc)
  - 1 yr, 12.4% vs. 12.9%
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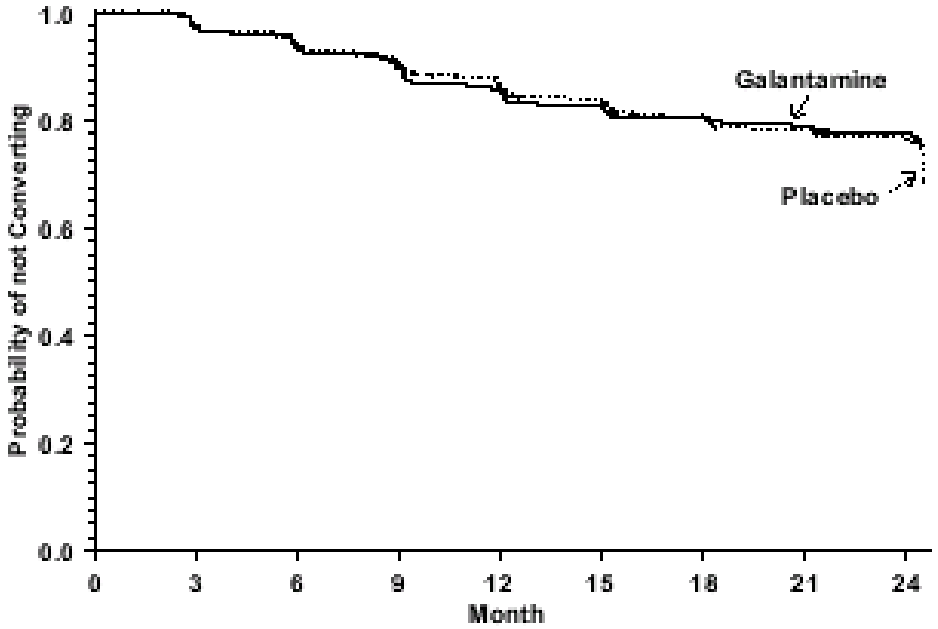
  - 168 vs. 126



Memory Impairment Study: Donepezil or Vitamin E Trial

- N = 769, 3 y follow-up
- Characteristics: 73 yr, 46% female, 55% APOE 4
- Total conversions: 212 (28%)
  - Median survival days: 661 (270) vs 484 (272)
  - Conversions: Donepezil 63, Vit E 76, Placebo 73
    - 1st yr: 14 donepezil vs 36 placebo
    - 2nd yr: 25 donepezil vs 18 placebo
    - 3rd yr: 24 donepezil vs 19 placebo
- Characteristics of converters
  - MMSE < 27
  - Age > 73
  - APOE 4 (more frequent in donepezil treated subjects
- Differential Discontinuations: 306 (40%)
  - 1st yr: 60% donepezil vs 46% placebo
  - 2nd yr: 22% placebo vs 44% placebo
- "Informative censoring"
- One outcome: Time to onset of dementia longer in donepezil
- Second outcome: Over 3 years no significant differences

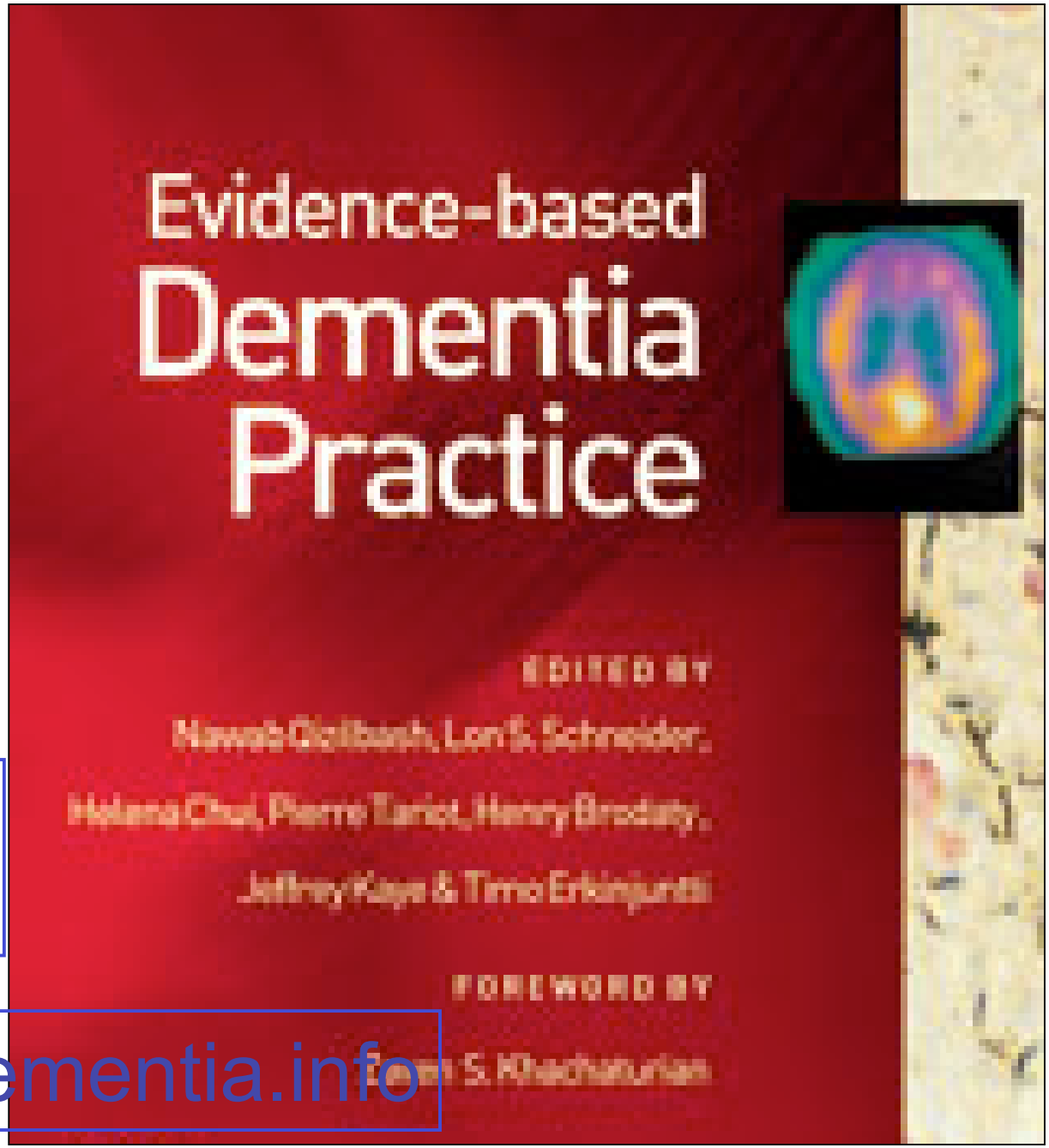
Funded by Pfizer and NIA

Petersen et al 2004 Philadelphia

Conclusions

- MCI is a moving target
  - Two groups: those who will get dementia and those who won't.
  - A group representing early AD before the dementia can be identified
  - Some MCI is AD
- Outcome measures for MCI trials are cognitive
- Relevant endpoints and intermediate outcomes remain to be resolved
- Biological markers are those for AD
  - Best predictors are hippocampal volume and APOE4
- MCI trials are interventions for early AD
- No guideline to MCI trials or claims
- Concerns about generalizability and clinical relevance
- Any positive results of current trials may both inform and misinform
- Dropouts are a challenge for assessing validity and outcomes
  - "All randomized subjects need to be analyzed"
- Then there are adverse events…
- Prevention trials are feasible
- Trials remain un-reported

END



Editors:
Qizilbash N, Schneider L
Chui HC, Tariot PN, Brodaty H,
Kaye J, Erkinjunti T

www.ebdementia.info

There are currently no standard therapies approved for use in MCI or as preventative AD treatments. The challenge for clinical researchers in the near future will be the development of well-designed trials with several key features. Studies that demonstrate efficacy for a particular therapeutic intervention must be double-blind and placebo-controlled. They will have to be long-term studies (5 or more years), with large cohorts (>3000 subjects), to determine the ability of a particular agent to prevent or delay AD onset. It may be easiest to test for an effect on conversion to AD in a population of MCI patients, as that patient population converts at a much higher rate than the general population. However, that strategy must consider the fact that several studies of cases of MCI reveal them to already have significant AD pathology.37–39 In addition, the population of subjects who would participate in such studies are relatively disease free, which means that an overwhelming emphasis must be placed on safety of treatment, especially during long-term therapy. Significant side effects that may be tolerated in a disease of short duration would not be tolerated during a 5-year trial, for instance. Finally, because of our current limited understanding of early events in the pathogenesis of AD and our inability to restrict diagnosis to only those who will eventually get AD, outcome measures for trials will need to focus on decreased rates of conversion to AD, as opposed to merely slowing decline in cognitive function. Despite these restrictions, the rationale for developing effective preventative treatments for AD is strong, and preventative trials with several relatively benign agents, including *Ginkgo biloba*, nonsteroidal anti-inflammatory drugs, and estrogen/progesterone, are now underway.

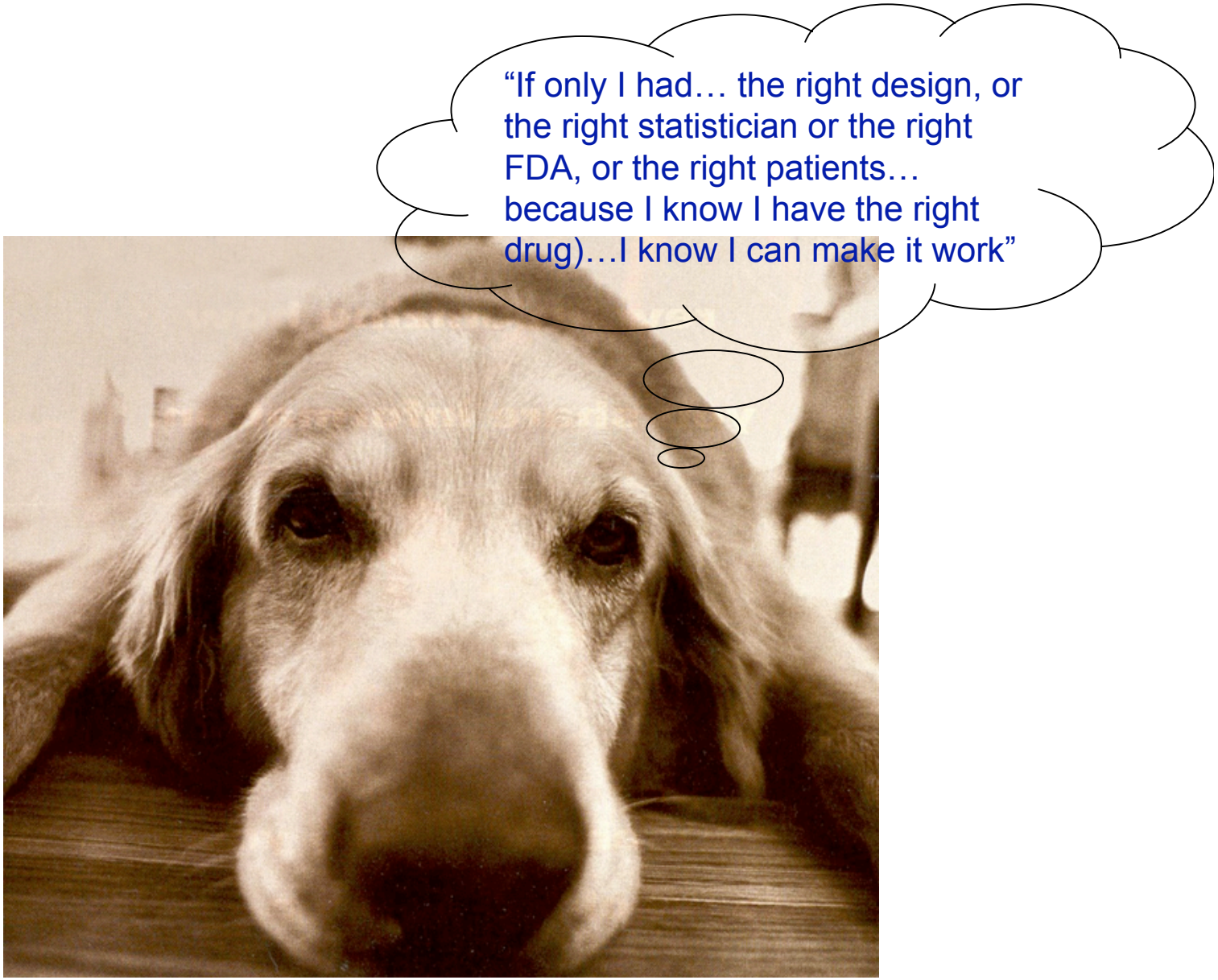
- those with mild AD, choline acetyltransferase (ChAT) activity
- is significantly higher in certain regions of the brain in subjects
- with MCI.39 This occurs specifically in the entorhinalhippocampal
- system, where pathologic changes have already
- occurred (in the entorhinal cortex) in MCI.40 The rise in ChAT
- activity may represent a compensatory response to hippocampal
- denervation resulting from neuronal deficits in the entorhinal
- cortex. Cholinergic function may be impaired early in
- AD,41,42 but actual loss of the synthetic enzyme does not occur
- until much later in the disease. Cholinesterase inhibitors appear
- appear
- to delay admission to nursing homes. Their application to
- MCI may similarly delay progression to AD, and clinical trials
- are underway in MCI patients.43,44
- Since it is clear that NFTs and amyloid plaques are present
- in many patients with MCI, current strategies aimed at reducing
- the deposition of amyloid and production of NFTs are
- valid interventional approaches. Amyloid immunization techniques
- are being explored in the hope of halting or possibly
- reversing some pathologic changes in AD, although a recent
- clinical trial was aborted due to serious adverse effects.45
- Agents that decrease the production or deposition of A, such
- as -secretase or -secretase inhibitors, or inhibit kinases responsible
- for the hyperphosphorylation of tau (thus slowing
- development of NFTs) also may lead to delayed disease progression.
- Statins, which have been associated with a reduced
- risk of AD in epidemiological studies, have been hypothesized
- to be involved in the alteration of -amyloid regulation, and at
- least two large clinical trials are underway in AD patients with
- this class of agents.
- Oxidative stress is another important factor in AD, and
- because antioxidative compounds such as vitamin E have been
- associated with some benefit in moderate AD,46 new trials are
- poised to test its effect on progression of MCI.47Arecent study
- suggested that CSF levels of an isoprostane, a marker of oxidative
- stress, are increased in MCI.48 Moreover, a correlation
- between increased isoprostane and progression of MCI was
- found. Thus, oxidative mechanisms also may play a role in
- MCI, making the study of antioxidants in delaying its progression
- an important focus. In addition to studies on vitamin E, the
- use of *Ginkgo biloba* extracts, another antioxidant, may prove
- beneficial in the delay of progression of AD.49,50
- Other agents that warrant attention are nonsteroidal antiinflammatory
- drugs, estrogen, and glutamate receptor modulators.
- Epidemiologic research suggests that the inflammatory
- response is a significant component of the pathology in AD.51

- CONCLUSION: TARGETING AD BEFORE
- THE DIAGNOSIS
- The latest developments in understanding AD pathology
- have come from the recognition that the course of the disease
- represents a continuum, both in pathology and cognitive abilities
- (Fig. 2).
- The identification of MCI as a prodromal AD represents an enormous opportunity for public health
- gains against AD. To that end, it is clear that continued MCI
- research can provide a clearer understanding of the complex
- interplay of cognitive, neuropathological, and functional deficits
- in AD. Although our definition and our ability to diagnose
- MCI are in their infancy, already there are diagnostic tools
- being developed which, with the power of longitudinal
- studies, will help to reach a high level of diagnostic accuracy
- while increasing our understanding of the pathology of each
- stage.
- Armed with the tools to evaluate potential treatments,
- the most effective therapies in the prevention of AD can be
- identified, providing additional hope for people at risk for AD.
- In a complex disease with multiple determinants, therapies
- will likely be multiple, as in heart disease or cancer. The search
- is underway.
- REFERENCES

- Geriatric psychiatrists are always standing between the audience and the bathroom
- The elephant!
- Several themes to be recounted
- It's the patient stupid!
  - What works for the patient?
  - Patient interests are often not understood or appreciated
  - No, if the patient would only take the medication properly
  - The goal is not to see what drug is effective but to see what makes a patient better
- It's the labeling…!
  - What the company can say about their drug?
  - Short term trials get the drug on the market but leave little room for companies to advertise
  - Companies always want to say more about their drug's safety and efficacy than they should (and so do academics)
  - Long-term trials might not satisfy the marketing needs
- It's the statistics…!
  - We need better statistics, or better statisticians?
  - We need survival designs!
    - (Proportionality assumption? What's that?)
  - We need non-inferiority designs
  - The clinical problem precedes design
  - Design precedes statistics
  - "Can't fix by analysis what is broken by design"
  - Data dredge at your own risk
- It's the design…!
  - If we just had the right design we'd be able to prove the drug is effective
- It's the FDA…!
  - Can't they tell us what to do?
  - How dare they tell us we can't do this!
- Academic interests may not coincide even with patient interests
- It's semantics!
- It's the drug…!
- No it's the collusion of competing interests
  - Industry development
  - Industry post-marketing
  - Regulatory issues are not necessarily clinical issues; they serve industry by regulating corporate free

Long term Trials Comments

- There is no one kind of long-term trial design
- But trials should be patient centered.
- Bipolar manic episodes as outcomes?
- Composite outcomes
- Integrate area under the curve
- A single trial does not provide a definitive answer
- A controlled clinical trial is a controlled experiment and can answer only one or two questions by holding several factors (artificially) constant
  - The control can be a placebo or usual care
  - May be because trials are less biased!
- Both industry and academics often look to regulators for guidance…"tell us what to do."
- Sharing data bases and data mining is of course a mine field
  - Fraught with mines
  - But examples from AD are Axonyx and Lundbeck.
- Lose track of whether we are treating patients or testing drugs, the two are different, but a good drug can drive out an inefficient design



"Evil, cream-sucking cats," cursed Zak. "If only I had access to the world's data banks on their wily ways, I could thwart their cunning. If only," he mulled, "if only…"

Gal -11 and -18 Outcomes

- N = 898
- Conversion
  - 1 yr, 6.6% vs. 11.5%
  - 2 yr, 13.3% vs. 18.4%
  - RR = 0.78 (0.6 to 1.1)
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  - RR = 0.93 (0.7 to 1.24)
- Dropouts
  - 168 vs. 126

Criteria for MCI in Trials

- Memory complaint, preferably corroborated by an informant
- Objective memory impairment
- Normal general cognitive function
- Intact activities of daily living
- Not demented

Petersen RC *et al*. Arch Neurol 1999; 56: 303–8