

# Clinical and Cognitive Features of DLB

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## Disclosure of Interest

### Research Support

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  1. NIA
  2. NIMH
  3. NACC
2. American Federation for Aging Research
3. Alzheimer's Association
4. Longer Life Foundation
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### Consultant

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### Licensing Agreements

Pfizer, Eisai, Novartis

I own no stocks or equity in any pharmaceutical company

# Dementia with Lewy Bodies

## Consensus Criteria for the Clinical Diagnosis

- Progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function
- Core features (2 → probable DLB; 1 → possible DLB)
  - Fluctuating cognition with variation in attention and alertness
  - Recurrent visual hallucinations
  - Parkinsonism
- Suggestive features (1 or more in addition to core features)
  - REM sleep behavior disorder
  - Neuroleptic sensitivity
  - Low dopamine transporter uptake in basal ganglia
- Supportive features (lack diagnostic specificity)
  - Repeated falls/syncope
  - Transient loss of consciousness
  - Severe autonomic dysfunction
  - Systematized delusions
  - Hallucinations in other modalities
  - Depression

# Clinical Dilemma

- Dementia of the Alzheimer type (DAT) is the most common cause of dementia, with DLB being the second most common neurodegenerative cause.
- Up to 1/3 of patients clinically-diagnosed AD patients coming to autopsy have sufficient cortical and limbic Lewy bodies to meet criteria for DLB. In nearly all of these cases, DLB was not considered as a possible clinical diagnosis
  - Our experience is similar to what has been reported in other samples such as the Florida Brain Bank (Barker et al, ADAD 2005).
- Propose: misclassification of DAT patients has significant implications in clinical trial enrollment, biomarker research, prognosis and treatment outcomes.

# Cognitive Fluctuation

- Most confusing aspect
- Spontaneous impairment: alertness/attention
- May appear drowsy but awake, look “dazed”
- Vary from day to day or week to week
- Loss of consciousness has been described
- No EEG correlate
- Mayo Clinic Fluctuation Scale (Ferman, 2005)
  - Drowsy or lethargic during day
  - Sleeps for 2 or more hours during day
  - Thinking illogical, unclear, incoherent
  - Stares into space

# Cognitive Features of DLB

Psychometric Test	Factor 1 (Visuospatial)	Factor 2 (Verbal)
WAIS Digit Symbol	.88	
Trailmaking A (seconds)	-.87	
WAIS Block Design	.87	
Benton Recall Correct	.78	
Benton Copy Correct	.77	
Crossing Off	.68	
WAIS Information		.85
WMS Logical Memory		.82
WMS Associate Memory		.82
Boston Naming Test		.75
WMS Digits Forward		.64
WMS Digits Backward		.58
Word Fluency		.56
% explained variance	38	32

*Longitudinal Sample (n=132)*  
66 AD, 57 DLB, 9 pure DLB

*Visuospatial factor*  
Pure AD = pure DLB > DLB/AD

*Verbal factor*  
Pure DLB > pure AD = DLB/AD

Suggests that cortical Lewy bodies alone are not associated with *verbal memory* deficits, but the presence of both AD and DLB produced poorer *visuospatial* performance than either pathological burden alone

# Personality Traits in DLB

Variable	Nondemented (N=34)	AD (N=125)	DLB (N=125)	p-value
Age at first visit (yrs)	80.6 (9.9)	78.1 (10.3)	76.4 (9.3)	ns
Age at diagnosis	84.4 (6.7)	81.8 (10.9)	80.8 (10.4)	ns
Age at death	91.9 (7.7)	84.4 (10.1)	81.7 (9.4)	.01
Gender (%men)	52.9	44.4	50.4	ns
Education	13.2 (4.2)	13.8 (3.5)	12.9 (3.5)	ns
# assessments	6.5 (7.0)	4.9 (3.9)	4.2 (3.4)	ns
CDR at 1 <sup>st</sup> visit	.07 (.18)	.56 (.47)	.85 (.60)	<.001
CDR-SB at 1 <sup>st</sup> visit	.33 (.85)	3.0 (2.9)	4.7 (3.7)	<.001
CDR at diagnosis	.31 (.26)	.59(.41)	.79 (.45)	<.001
CDR-SB at diagnosis	1.2 (1.3)	3.2 (2.7)	4.5 (3.0)	<.001

**Blessed Dementia Scale:** Rigidity, Egocentricity, Loss of Concern, Coarse Affect, Impaired Emotional Control, Inappropriate Hilarity, Diminished Emotion Responsiveness, Sexual Misdemeanor, Relinquish Hobbies, Apathy, Purposeless Hyperactivity

**Other Behaviors:** Hallucinations, Delusions

# Analysis of Personality Traits

Variable	Factors		
	Irritable	Passive	Disinhibited
Increased rigidity	.728		
Increased egocentricity	.813		
Loss of concern	.753		
Coarsening of affect	.494		
Impaired emotional control	.428		
Diminished emotional responsiveness		.663	
Hobbies relinquished		.823	
Growing apathy		.805	
Purposeless hyperactivity		.476	
Hilarity			.632
Sexual misdemeanor			.814
<b>Rotated Eigenvalues</b>	<b>4.1</b>	<b>1.1</b>	<b>1.1</b>
<b>Explained variance (%)</b>	<b>37.5</b>	<b>10.4</b>	<b>10.1</b>

## Area under ROC curve

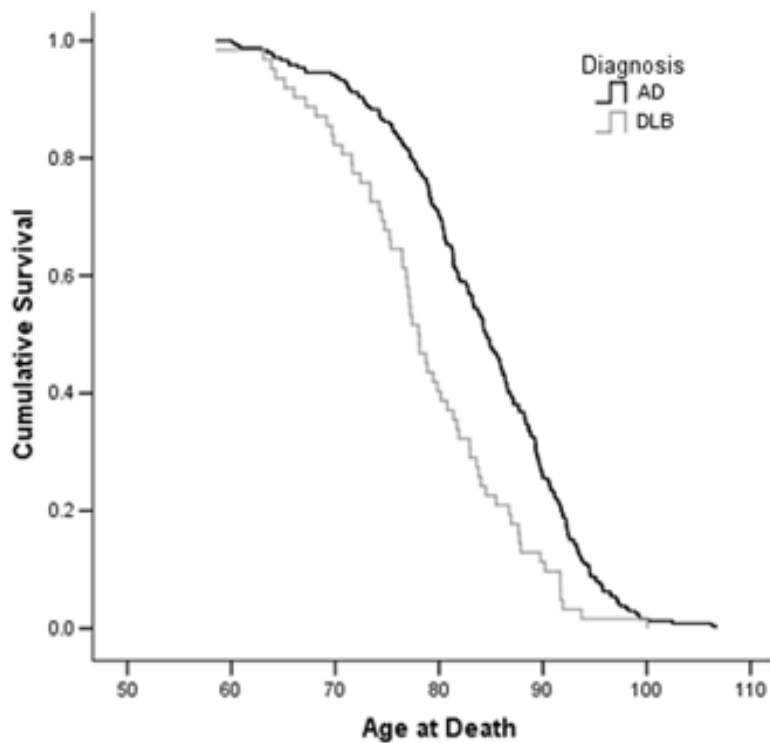
PASSIVE: AUC = 0.61 (95% CI: 0.54-0.68, p=.006)

This suggests good ability to discriminate between DLB and AD.



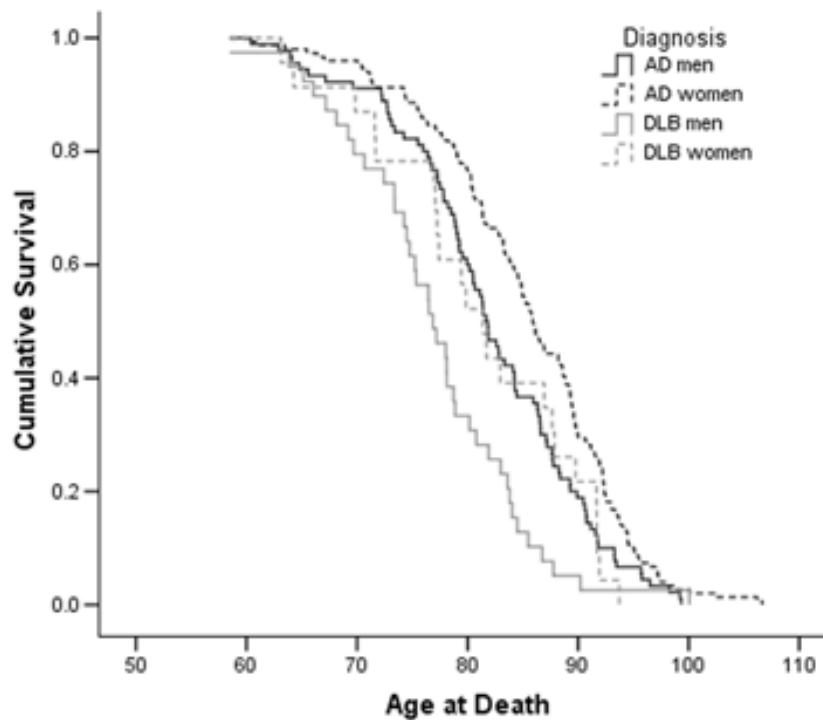
# Outcome Analyses: Mortality

## A



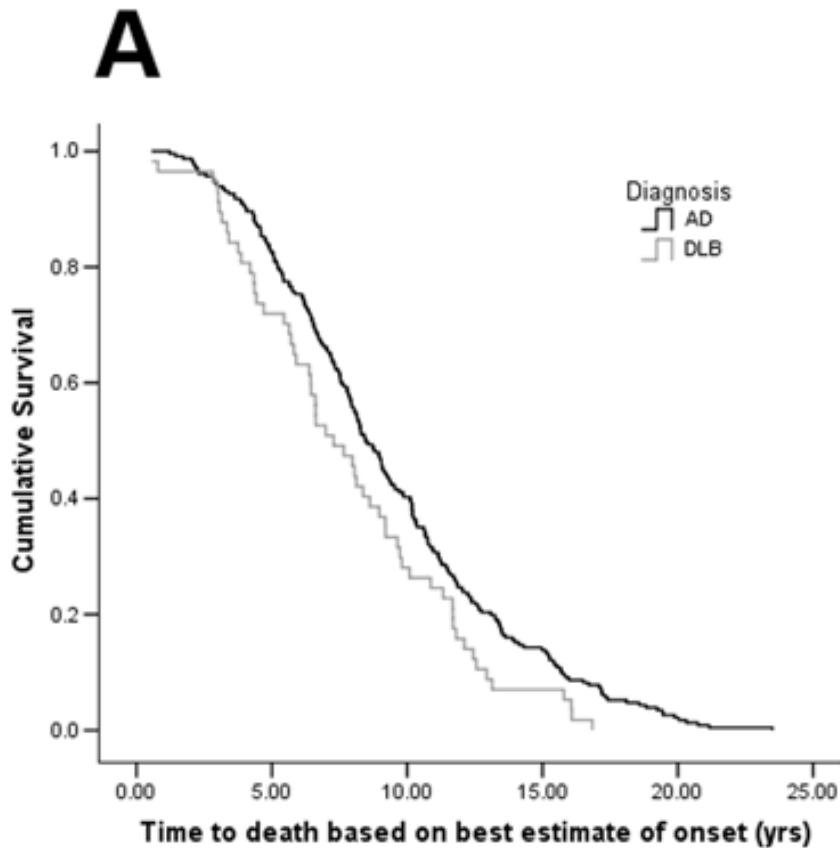
DLB: 78.0y  
AD: 84.6y  
( $p < 0.001$ )

## B

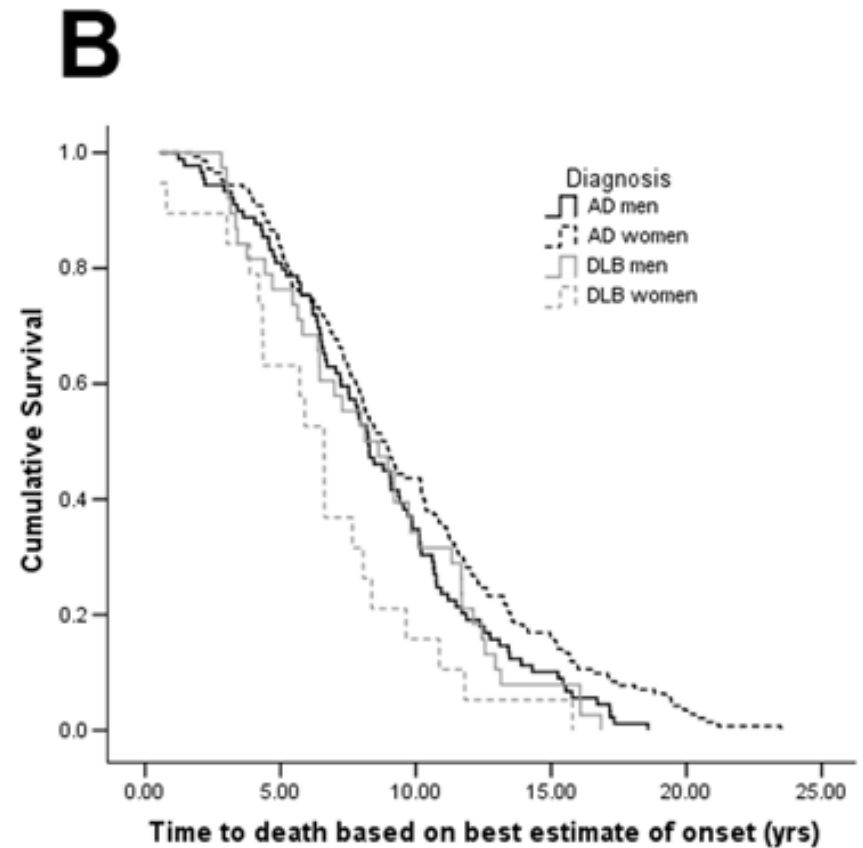


DLB men: 76.8y  
AD women 85.9y  
( $p < 0.001$ )

# Outcome Analyses: Survival post-Dx



DLB: 7.28y  
AD: 8.47y  
( $p=.02$ )



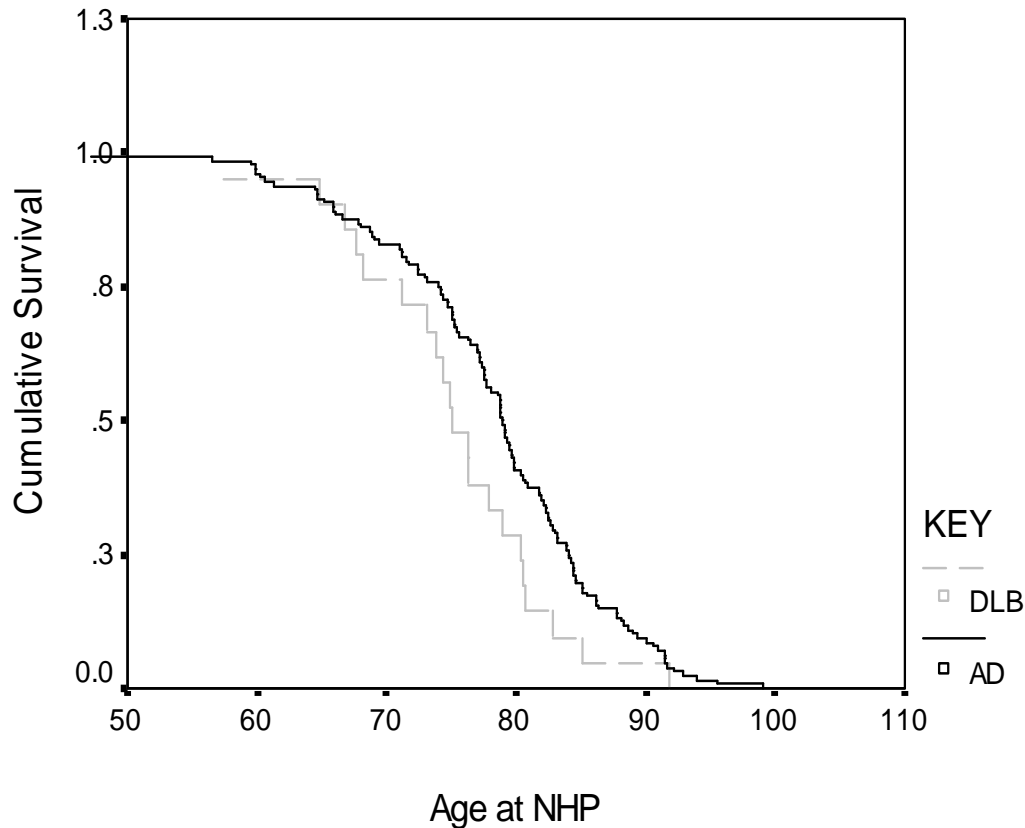
DLB women: 6.61y  
AD women: 8.75 yrs  
( $p=.005$ ).

# Results: Adjusted HR (Survival)

- Rest tremor (present in 35 individuals) was a protective factor related to survival
  - HR 0.29, 95% CI: 0.14-.63
- This finding suggests that rigid-predominant forms of parkinsonism in dementia may lead to worse outcomes, similar to risks reported for rigid-predominant forms of PD

# Outcome Analyses: NH Placement

Survival Time to NHP

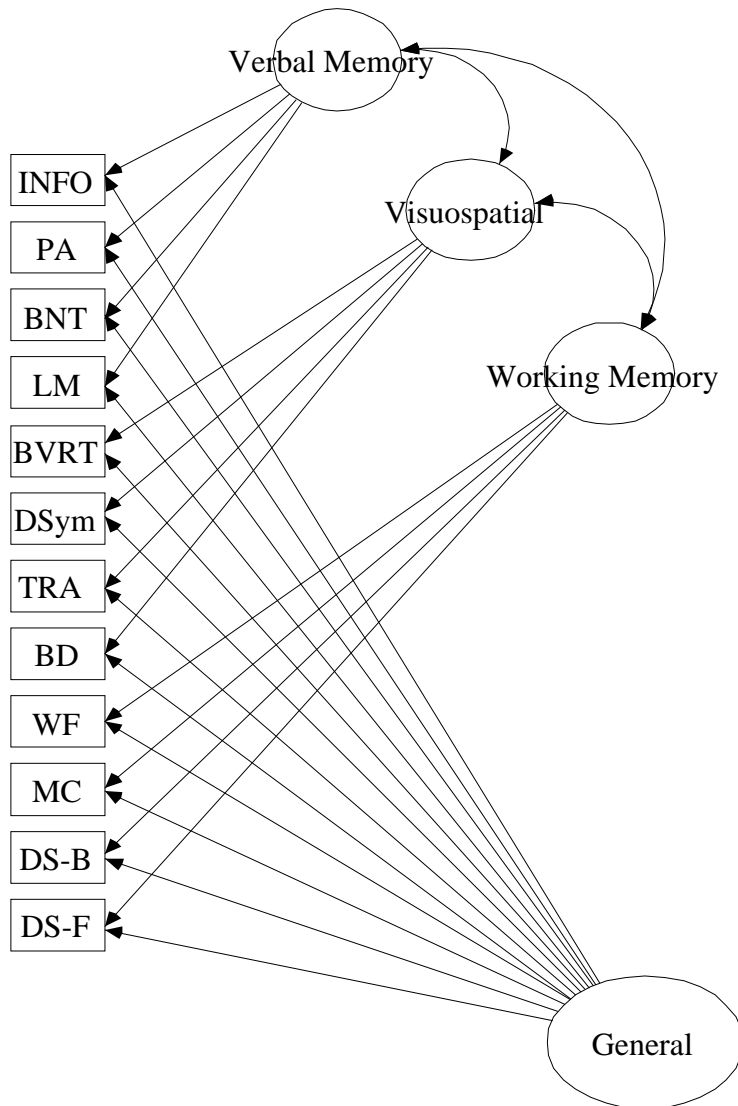


- Marginal difference in placement
  - DLB vs. AD ( $p=0.07$ ).
- NH placement median time
  - DLB: 6.1y (95% CI: 4.4-7.8)
  - AD: 6.6y (95% CI: 5.9-7.2).
- Covariates:
  - Self-report depression: HR 1.66
    - 95% CI: 1.1 - 2.6
  - Extrapyrimal signs: HR 22.96
    - 95% CI: 1.8 - 288.5
- No gender effect.

# Outcome Analyses: Survival in NH

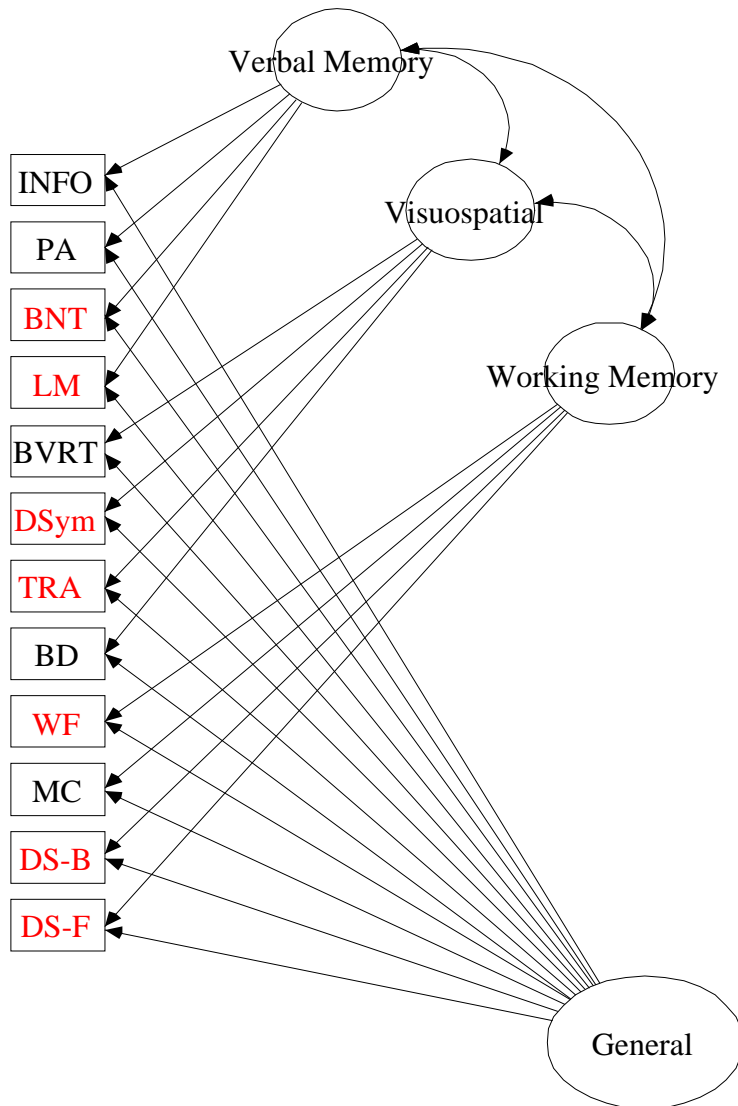
- Marginal difference in the survival time in a nursing home to death between AD and DLB ( $p=0.08$ ).
- DLB median survival: 28.93 months (95% CI: 14.4-43.6)
- AD median survival: 38.57 months (95% CI: 30.5-46.6)
- Gender effect ( $p = .012$ )
  - DLB women surviving shortest
    - median survival 12.17 months, 95% CI: 9.5-14.8
  - AD women surviving longest
    - median survival 41.30 months, 95% CI: 30.5-52.09
- Covariates
  - Depression (HR 1.69, 95% CI: 1.0 - 2.7)
  - Ability to feed self (HR 3.53, 95% CI: .96 – 13.0)

# Cognitive Profiles in Dementia



WAIS Information  
WMS Associate Recall  
Boston Naming Test  
Logical Memory  
Benton Visual Recall  
WAIS Digit Symbol  
Trailmaking A  
WAIS Block Design  
Category Fluency – Animals  
WMS Mental Control  
Digit Span – Forward  
Digit Span - Backward

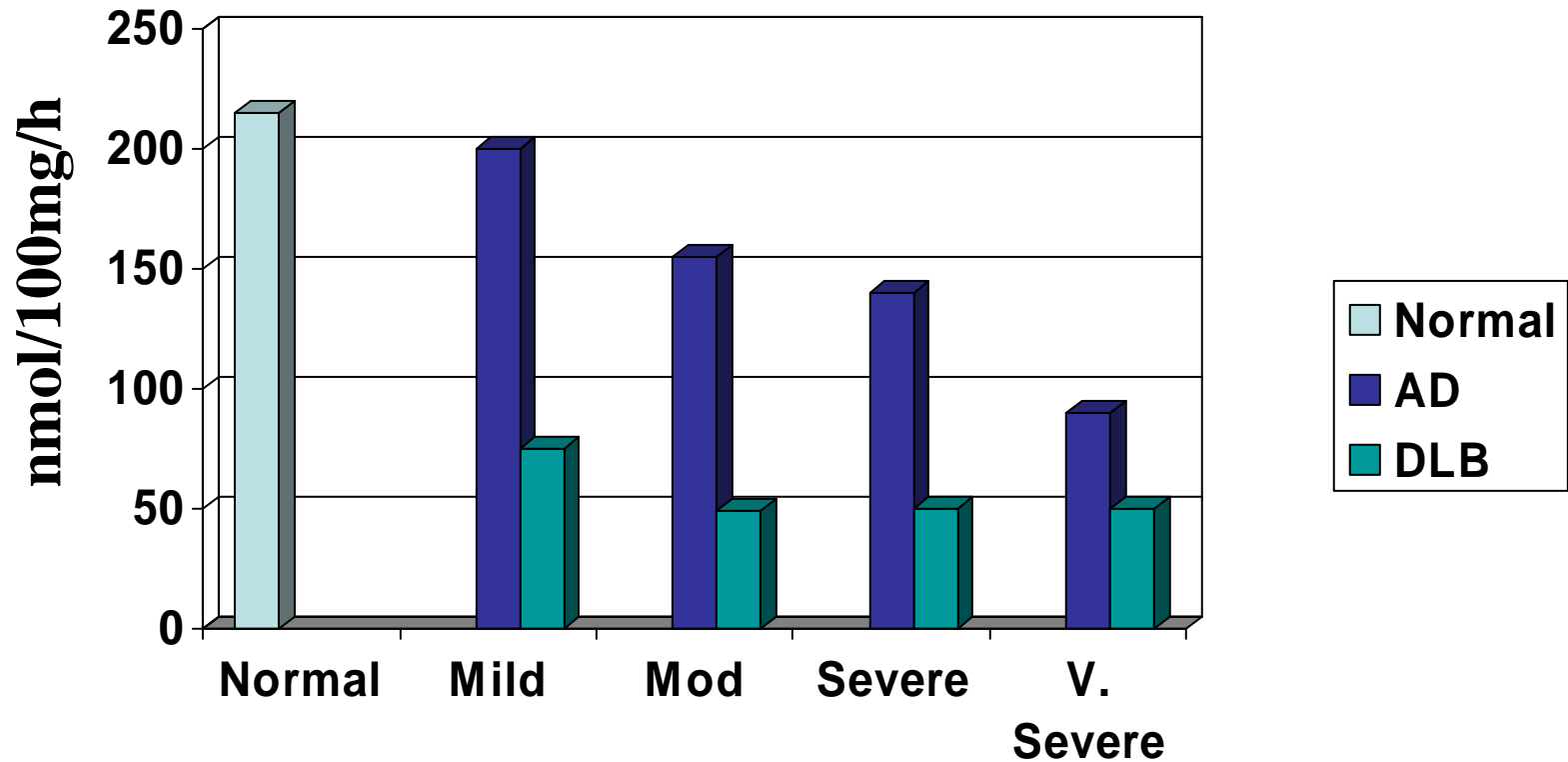
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# ChAT activity in AD and DLB

Midfrontal cortex



Adapted from Corey-Bloom (personal communication)



# Treatment Options

- No Approved Therapies
- Central Acting Cholinesterase Inhibitors
  - modest improvement in cognition
  - diminished hallucinations
  - improvement in behavior
- Role of Memantine is unclear
- For EPS: regular Carbidopa/Levodopa
- For RBD: Clonazepam, Melatonin
- Orthostatic hypotension: leg elevation, elastic stockings, increasing salt and fluid intake
  - Medication: midodrine, fludrocortisone
- Urinary urgency, frequency and incontinence
  - Medication: oxybutynin, tolterodine tartrate, bethanechol chloride, propantheline

# Psychotropics and Behavioral Disorders

- No FDA-approved orally administered agents for behavioral disturbances in dementia

Agitation	Psychosis	Depression
<ul style="list-style-type: none"><li>• Atypical antipsychotics*</li><li>• Mood stabilizers/anticonvulsants</li><li>• Antidepressants, anxiolytics, etc</li></ul>	<ul style="list-style-type: none"><li>• Atypical antipsychotics*</li></ul>	<ul style="list-style-type: none"><li>• SSRIs</li><li>• SSRNIs</li></ul>

**\*FDA Public Health Advisory (April 2005): Clinical trials of antipsychotic drugs to treat behavioral disorders in elderly patients with dementia have shown a higher death rate compared to placebo. SSRIs = selective serotonin reuptake inhibitors; SSRNIs = selective serotonin and noradrenergic reuptake inhibitors.**

Tariot PN. *J Am Geriatr Soc.* 2003;51(5 suppl Dementia):S305-S313.

# Conclusions

- DLB has a more rapid progression than AD in general cognitive abilities and differences exist in domain-specific cognitive abilities
  - Verbal Memory: Preclinical AD has a more rapid change; after diagnosis rates of change are similar between AD and DLB
  - Visuospatial abilities: Preclinical DLB is already at floor effect, better visual-spatial tasks are needed to describe deficits in DLB
  - Working Memory: After diagnosis, DLB progresses at a more rapid rate
- DLB also has a more rapid progression in clinically-meaningful outcomes such as mortality, survival and nursing home placement.
  - non-cognitive features of depression, extrapyramidal signs, inability to carry out ADLs are important covariates.
- As there are no batteries specifically designed to detect DLB, assessing personality traits, psychotic features, sleep and fluctuations may improve the clinical diagnosis of DLB.
- The findings underscore the importance of accurate antemortem diagnosis, understanding the differences in clinical and cognitive features and how these differences might impact what we learn from clinical trials, longitudinal studies and biomarker research projects

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