Lewy body dementias – target population and specific end points.

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Talk Plan

- Terminology
- Diagnostic Criteria
- Epidemiology
- Theraputic needs / targets
- Trial populations
- Predictors of Outcome
- Side effects
- Summary

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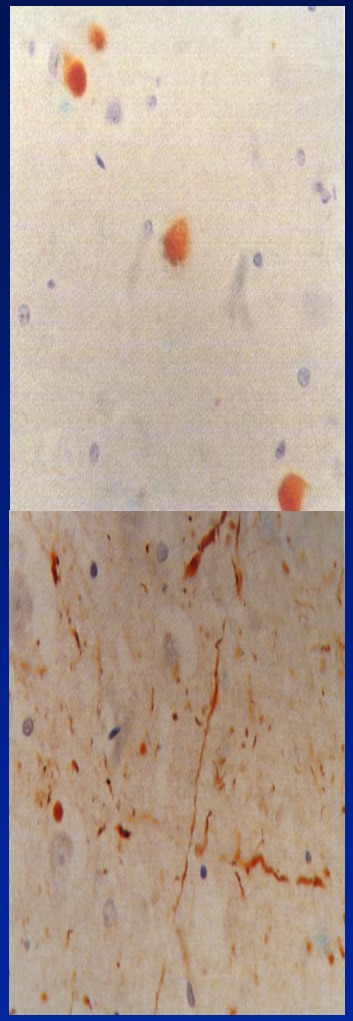
Lewy Body Disorders



Parkinson's Disease

Lewy Body Dementias

PD Dementia

Dementia with Lewy Bodies (DLB)

50 -60 Increasing age 70 - 80

Diagnostic Criteria for PD dementia

(Emre M et al, Movement Disorders 2007 2007 Sep 15;22(12):1689-707)

- Parkinson's disease
- Dementia
  - > 1 cognitive domain
  - ADL > motor and autonomic deficits
- Associated clinical features
  - Cognitive – attention, executive, visuospatial, memory, language
  - Behavioural – apathy, personality and mood, hallucinations (v), delusions, daytime sleepiness
- Exclusions include other conditions causing confusion or unknown time course of motor/cognitive symptoms

Can diagnose probable or possible PDD

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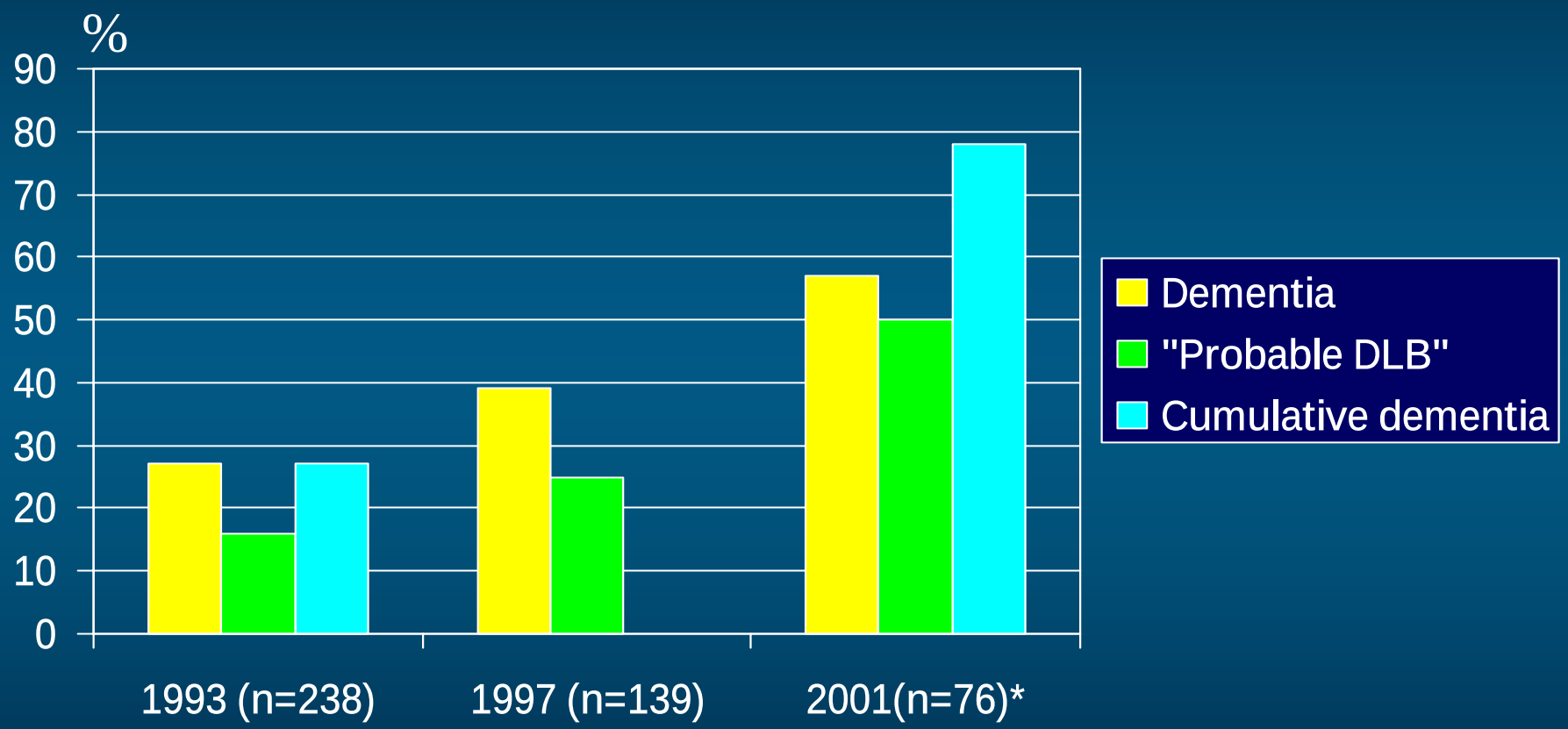
Dementia in PD

(Aarsland et al, Arch Neurol 2003; 60: 387-392)



Mean time from onset of PD to dementia is 10.5 yr (range 4-27) **(Apaydin et al, 2002)**

Diagnostic Criteria for DLB

McKeith et al, Neurology, 2005

- **Cognitive decline & reduced social/occupational function**
  - Attentional, executive and visuo-spatial dysfunction prominent
- **CORE features**
  - Fluctuation
  - Recurrent visual hallucinations
  - Spontaneous parkinsonism
- **Suggestive features:**
  - REM sleep behaviour disorder
  - Neuroleptic sensitivity
  - Dopaminergic abnormalities in basal ganglia on SPECT/PET

At least one core + one suggestive or 2 core features for Probable DLB

One core or suggestive feature sufficient for Possible DLB

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How common is DLB?

- **Several post-mortem studies confirm DLB as second most common degenerative pathology after AD**
- **Prevalence around 15% in autopsy samples**
- **Few good epidemiological studies of DLB**

Stevens et al (2001):

- Community sampling of 1085 over 65's in London
- Mean age 75y, prevalence of dementia 10%
- 72 of the 107 cases could be given a subtype diagnosis
  - **10% probable DLB**
  - **31% probable and possible DLB**

DLB and PDD are similar with respect to:

- Cognitive profile
- Fluctuating cognition
- Extrapyramidal features
- Neuropsychiatric symptoms
- Neuroleptic sensitivity
- Response to cholinesterase inhibitors
- LB distribution and density
- Cholinergic and dopaminergic deficits

Diagnostic Accuracy for DLB and PDD

- Several autopsy studies confirm DLB diagnosis is 90%+ specific at autopsy.
- New DLB criteria have increased sensitivity and can be improved by imaging biomarkers
- PD dementia criteria are too new to have been validated. Sensitivity and specificity will depend on the severity of cognitive impairment - cf MCI and AD

Treatment needs in LB dementias

- **DLB causes significantly greater functional disability than Alzheimer's disease**
  (McKeith et al, *Am J Ger Psychiat 2006;14.7 582-588*)

- **Care costs of DLB are twice those for Alzheimer's disease**
  (Boström et al, 2007 Int J Ger Psychiat. 22:713-719)

- **Quality of life for people with DLB is significantly worse than for AD with 1 in 4 caregivers rating DLB as worse than death!**
  (Boström et al, 2007 Alz Dis Ass Dis 21: 150-154)

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Treatment targets in LB dementias

- General principles apply as for Alzheimer's i.e.
  - Symptomatic / disease modifying / primary prevention
  - Length of trial
  - Cognitive / global / functional outcomes
- Need to use different / adapted outcome measures
- Biomarkers exist to help diagnose DLB/PDD but none as outcome measures
- Need to decide whether to treat PDD and DLB as separate populations or whether to pool them.
- Placebo comparator may be more difficult than in Alzheimer's disease

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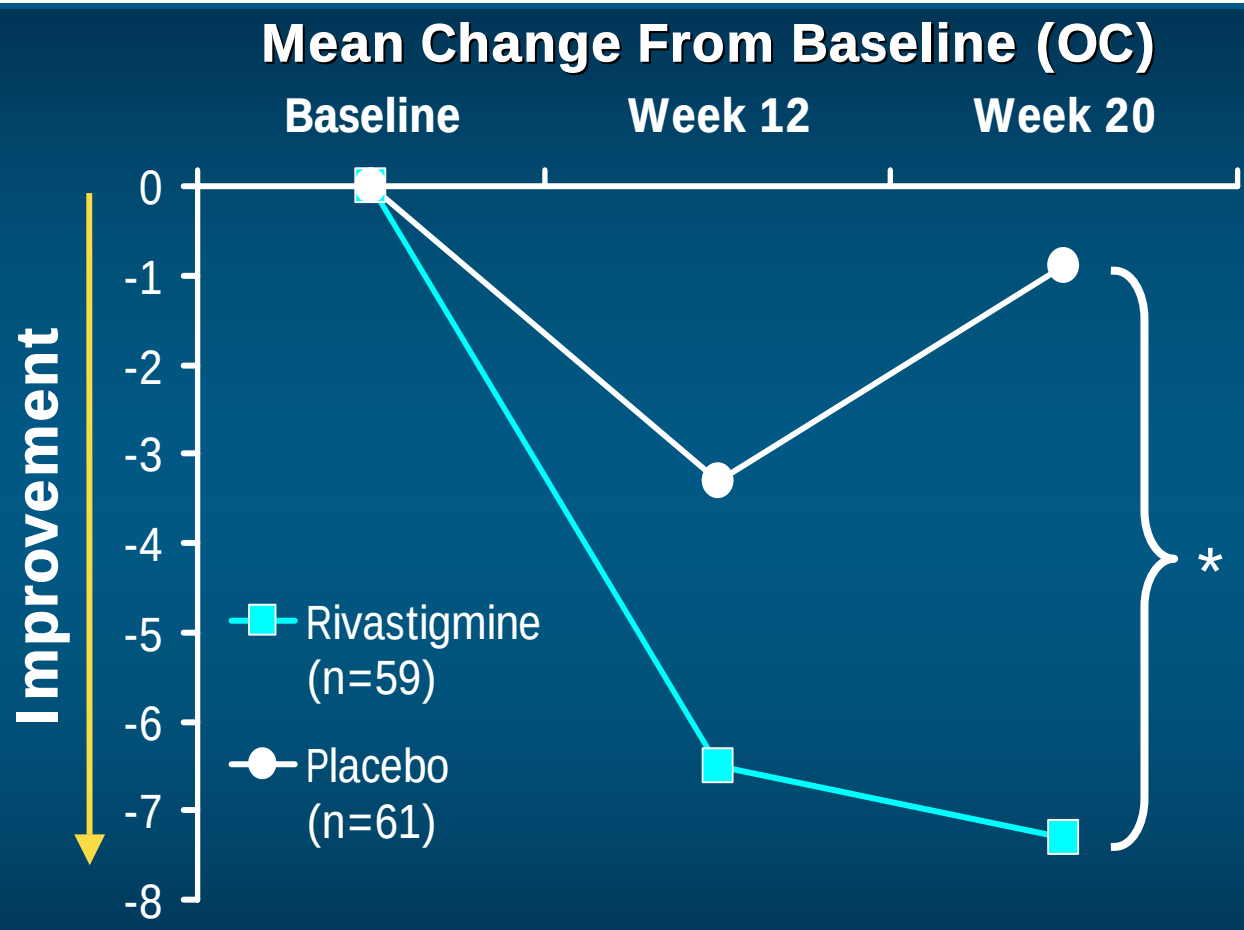
NPI Scores in a Placebo Randomized Controlled Trial of Rivastigmine in DLB



Mean MMSE ~17.

*P<.01 (ANOVA/ANCOVA).

McKeith et al. *Lancet*. 2000;356:2031-2036.

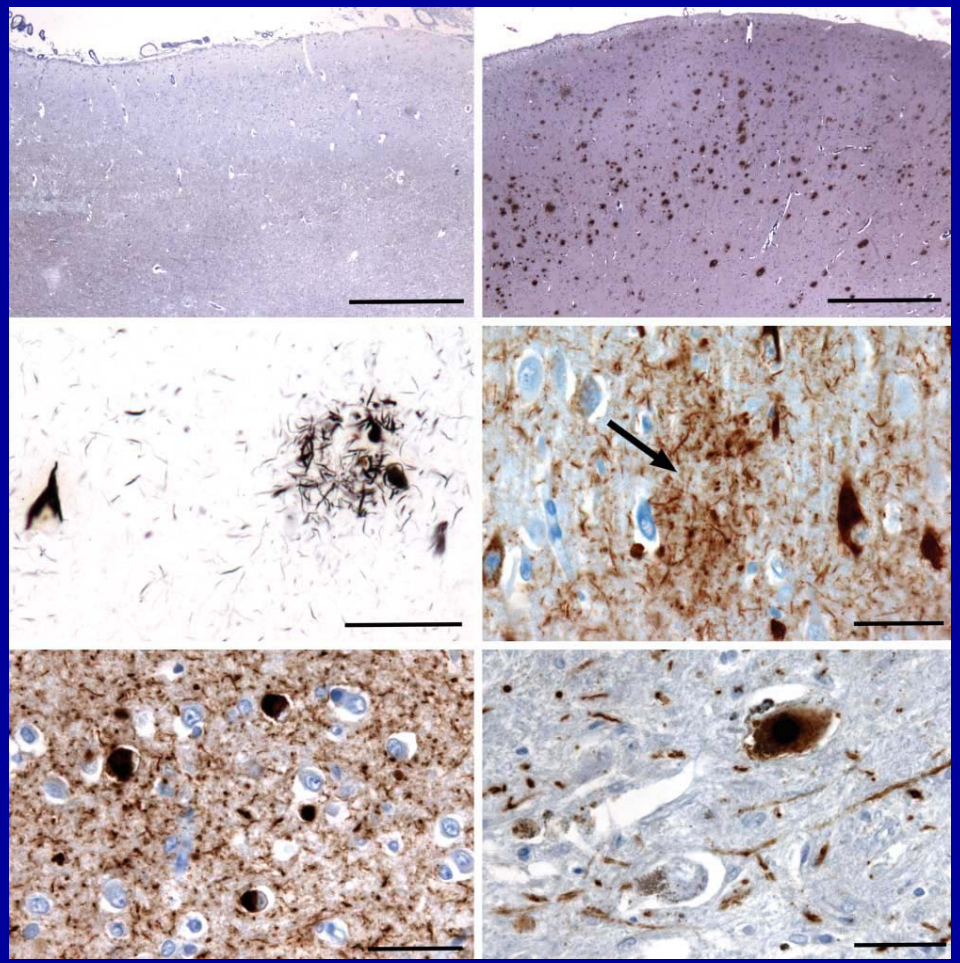
Absence of -Amyloid Deposits After Immunization in Alzheimer Disease With Lewy Body Dementia

Stephanie Bombois, MD; Claude-Alain Maurage, MD, PhD; Marie Gompel,PhD; Vincent Deramecourt, MD;Marie-Anne Mackowiak-Cordoliani, MD; Ronald S. Black, MD; Rodolphe Lavielle, MD; Andre´ Delacourte, PhD; Florence Pasquier, MD, PhD 2007 Archives of Neurology;64(4)583-587

Amyloid immunolabelling
Case /Alzheimer control

NFT and plaque corona / tau immunostaining

α-synuclein in temporal cortex / Lewy bodies and neurites



Targets and Outcome Measures

Domain	AD instrument	LB dementias
Cognition	ADAScog	Mattis DRS
	MMSE	CDR
Global	CIBIC	Extended CIBIC
ADL	DAD	Adapted ADL
Psychiatric	NPI	NPI
Motor	Not done	UPDRS III
Sleep	Not done	Epworth/Pittsburgh
Autonomic	Not done	Autonomic battery

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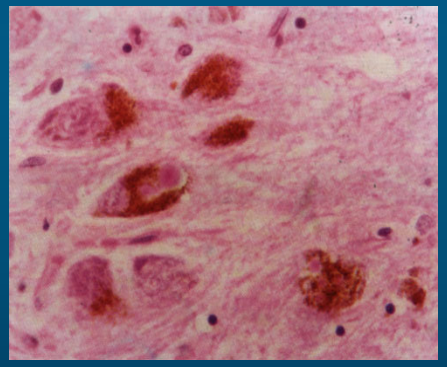
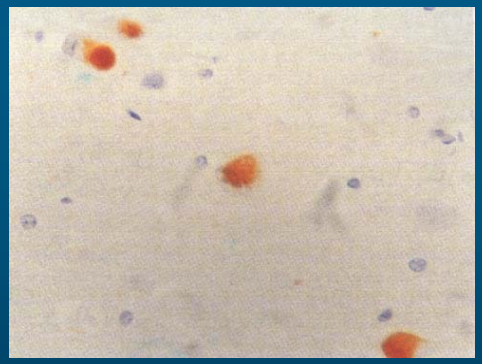
DLB and PDD Working Group Symposium: Boundary Issues and Future Priorities

Lippa et al (2007) Neurology 68:812-819

PD ~ 10 years PDD 1 year DLB





onset age 65y

onset age 75y

"DLB and PDD Working Group Symposium: Boundary Issues and Future Priorities

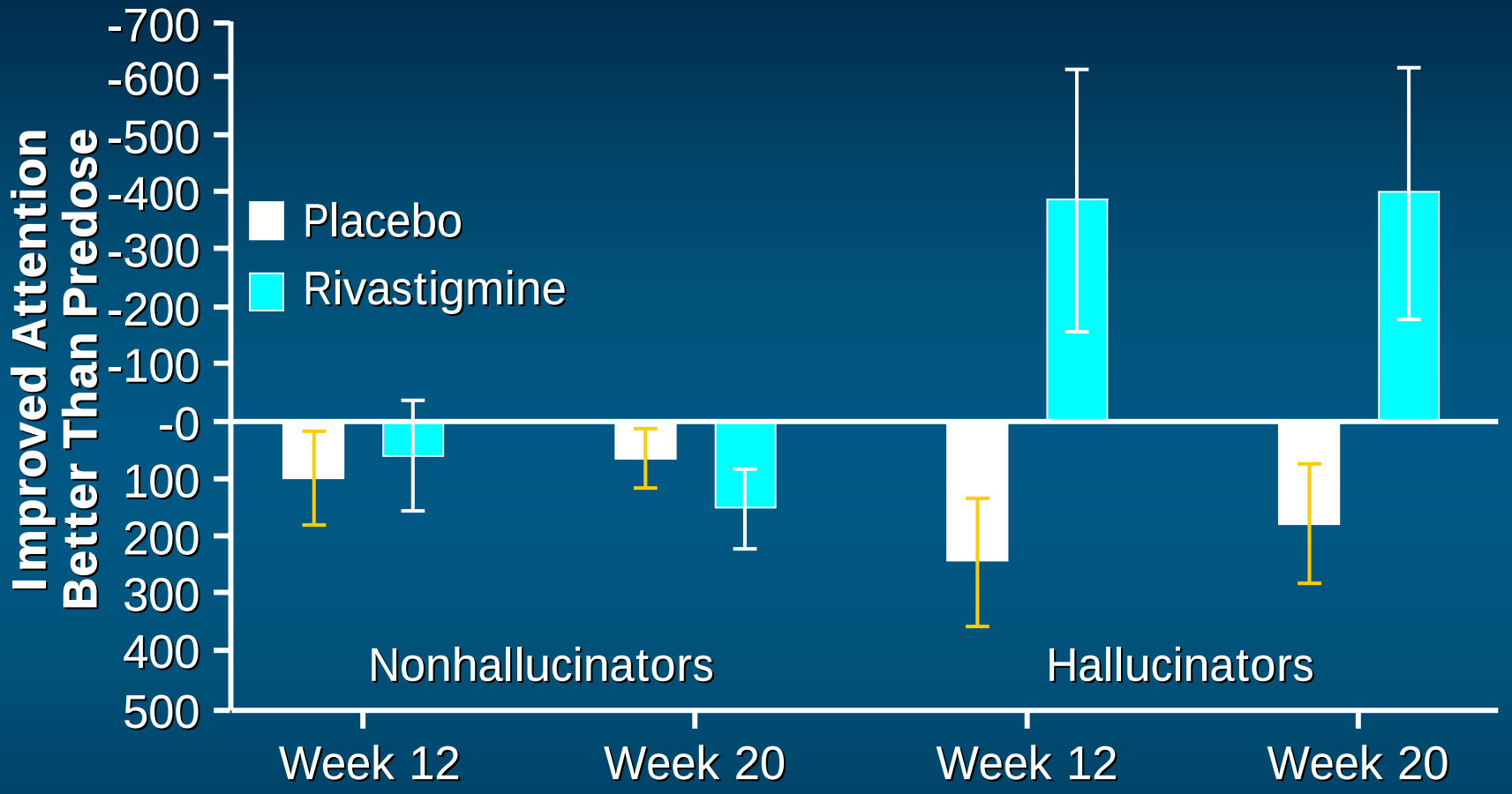
Lippa et al (2007) Neurology 68:812-819

Report of an NINDS sponsored meeting held in Washington DC in Feb 2006

"The differing temporal sequence of symptoms in PDD and DLB and differences in clinical features between these groups justifies the value of maintaining the clinical distinction between these entities"

A single "Lewy body disorder" model is deemed more useful for studying disease pathogenesis since "abnormal neuronal alpha-synuclein inclusions are the defining pathological process common to both PDD and DLB."

COGDRAS Speed of Attention

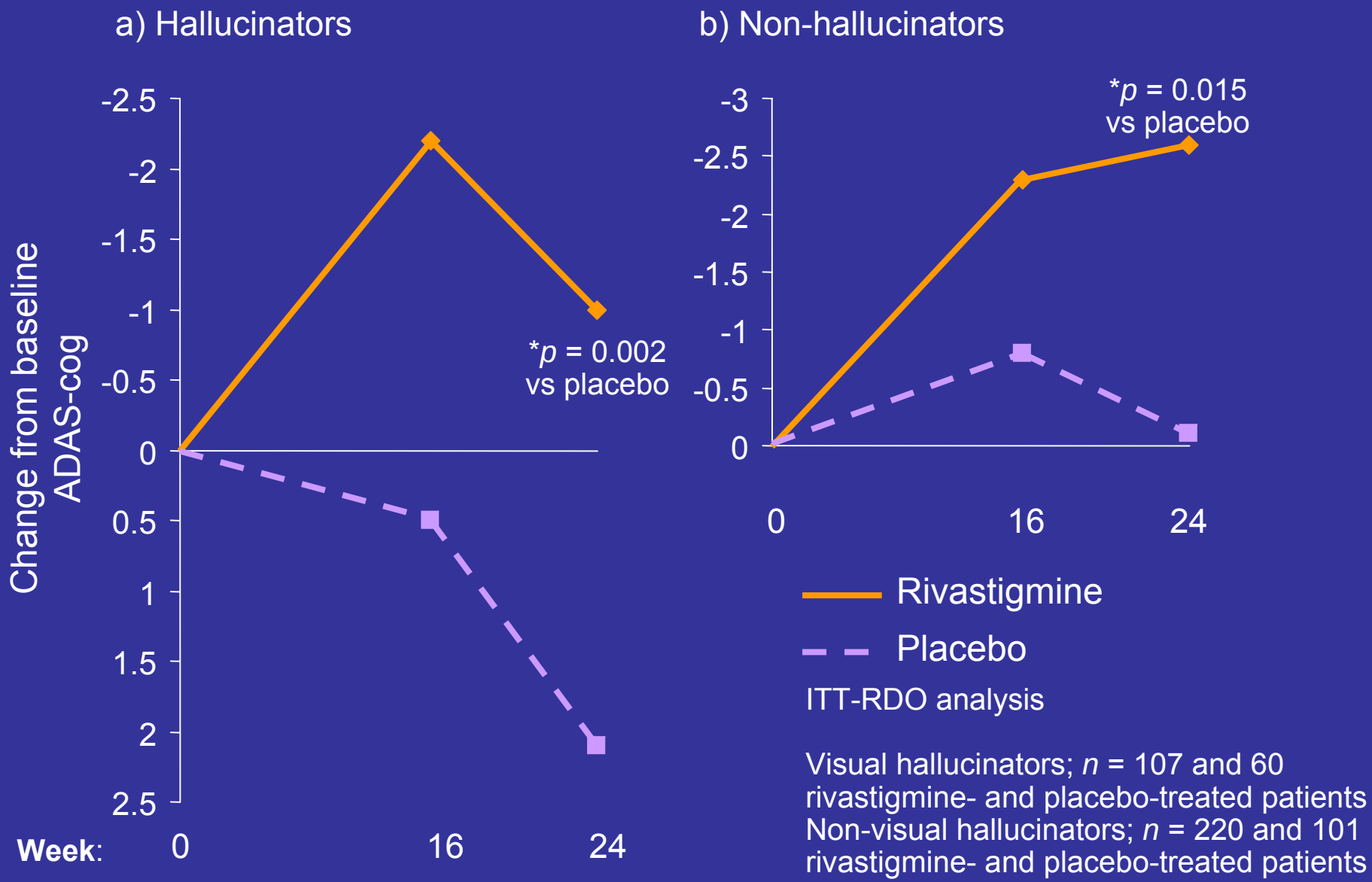


Hallucinations predict treatment response in DLB

McKeith et al. *Dement Geriatr Cogn Disord*. 2004;18:94-100.

PD EXPRESS study – rivastigmine in PDD

(Emre et al, New Eng J Med 2004)



ITT-RDO analysis

Visual hallucinators; *n* = 107 and 60 rivastigmine- and placebo-treated patients
Non-visual hallucinators; *n* = 220 and 101 rivastigmine- and placebo-treated patients

Side-Effect		Side-effect on 5mg	Side-effect on 10mg
Hypersalivation		9%	15%
Increased Lachrymal Secretions		0%	15%
Urinary Frequency/ incontinence		11%	4%
Nausea/vomiting		11%	7%
Dizziness/falls		4%	9%
Worsening Parkinsonism		3%	9%

No difference in side effect profile between DLB & PDD

A Comparison of the Efficacy of Donepezil in Parkinson's Disease with Dementia and Dementia with Lewy bodies Thomas et al Int J Psych 2005 20: 938-944

30 DLB and 40 PDD patients treated for 20 weeks

69% reached 10mg

Mean Δ MMSE
3.9 DLB and 3.2 PDD

Mean Δ NPI
14.6 DLB and 12.0 PDD

Quetiapine for agitation or psychosis in patients with dementia and parkinsonism

Kurlan, Roger MD; Cummings, Jeffrey MD; Raman, Rema PhD; Thal, Leon MD†; For the Alzheimer's Disease Cooperative Study Group Neurology 200768:17 1356-1363

- Quetiapine titrated by 25mg every 2 days to 150mg max
- CHEIs allowed
- BPRS primary outcome

Table 1 Baseline clinical characteristics

Features	Quetiapine (n = 20)	Placebo (n = 20)
M/F	11/9	14/6
Age, y	73.5 (5.8)	74.1 (6.1)
Alzheimer disease	4	4
Parkinson disease + dementia	5	4
Dementia with Lewy bodies	11	12
Duration of dementia, y	4.3 (2.4)	3.6 (2.3)
Cholinesterase inhibitor use	9	14
Dopaminergic drug use	7	8
Test scores		
BPRS	26.5 (8.7)	26.5 (8.5)
NPI	25.1 (18.1)	25.9 (15.6)
UPDRS-Motor	17.2 (7.5)	17.5 (7.1)
MMSE	19.2 (6.5)	17.2 (5.9)
ADCS-ADL	47.9 (16.7)	37.7 (19.1)

Values are n or mean (SD).
BPRS = Brief Psychiatric Rating Scale; NPI = Neuropsychiatric Inventory; UPDRS-Motor = Unified Parkinson's Disease Rating Scale-Motor Section; MMSE = Mini-Mental State Examination; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living.

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Table 2 Summary of primary and secondary outcome measures: Intent-to-treat results comparing quetiapine and placebo groups*

	Quetiapine, mean (SD) (n = 19)		Placebo, mean (SD) (n = 17)		Quetiapine − placebo (95% CI)† (n = 36), adjusted between group difference‡
	Baseline	Last observation	Baseline	Last observation	
Primary outcome					
BPRS	26.8 (8.8)	18.6 (8.9)	27.2 (8.7)	21.0 (7.6)	−2.2 (−7.1, 2.7)
Secondary outcomes					
UPDRS	17.2 (7.7)	18.0 (8.4)	17.9 (7.2)	18.5 (7.8)	0.2 (−2.4, 2.7)
NPI	25.6 (18.5)	24.6 (19.1)	27.7 (16.2)	26.6 (20.3)	−0.8 (−12.2, 10.5)
ADL§	47.0 (16.6)	40.5 (16.8)	38.5 (19.0)	36.8 (21.3)	−2.8 (−9.8, 4.2)
MMSE	19.1 (6.6)	18.0 (6.2)	16.8 (5.7)	16.6 (7.5)	−0.1 (−2.9, 2.6)
R-MDS-D, Parkinsonism	4.4 (2.1)	4.5 (2.2)	4.6 (1.8)	4.7 (2.1)	0.1 (−0.7, 0.9)
R-MDS-D, Pseudoparkinsonism§	2.3 (2.4)	3.2 (3.1)	2.1 (2.5)	2.4 (2.9)	0.2 (−1.3, 1.6)
ADCS-CGIC, %					
Moderate to marked improvement	—	10.5	—	17.6	1.5 (0.5, 4.5)
Minimal improvement		15.8		17.6	
No change	—	36.8	—	35.3	
Minimal worsening	—	21.1	—	17.6	
Moderate to marked worsening	—	15.8	—	11.8	

Values are means (SD) of unadjusted scores at baseline and at last visit. Imputation method was the last observation carried forward (LOCF).
*Four patients were excluded from the analysis since they did not have a post-baseline measurement.
†The estimate and 95% CI for ADCS-CGIC reflect ORs from the ordinal logistic regression analysis. All other estimates reflect results from the final analysis of covariance model.
‡Adjusted between-group differences reported as coefficient for quetiapine treatment arm vs placebo from final analysis of covariance model.
§Additionally adjusted for anticholinesterase use at baseline.
BPRS = Brief Psychiatric Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale; NPI = Neuropsychiatric Inventory; ADL = activities of daily living; MMSE = Mini-Mental State Examination; R-MDS-D = Rochester Movement Disorders Scale for Dementia; ADCS-CGIC = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change.

No significant changes in any measures from baseline to 10 weeks

No differences between quetiapine and placebo

Quetiapine did not worsen parkinsonism but was associated with a trend to reduced ADL function

? large placebo effect

? dosing too low

? underpowered

Lewy body dementias: Summary

- Internationally agreed diagnostic criteria exist for DLB and PDD
- Goals of treatment are similar to those for AD
- There are more treatment targets than in AD
- Outcome measures exist for most domains but differ slightly from AD
- Treatment effects in DLB and PDD are likely to be similar so trial populations may be pooled
- Demonstrating differences between DLB and PDD would require very large samples

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