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Design of trials in DLB and PDD

• What has been learnt from previous trials in these indications and other dementias?
• Overview of designs to date
• Challenges faced – patient selection
• Role of biomarkers, neuroimaging, neuropsychology
• Relevant lessons from studies in other dementias
• The Future
Lewy Body Disease

Parkinson’s Disease

PD Dementia

Dementia with Lewy Bodies (DLB)

Lewy Body Dementias
Lewy Body Dementias (DLB and PDD)

- Estimated 4M people affected worldwide
- Diagnostic criteria agreed globally for
  - PD (1992)
  - PDD (2007)
  - PD-MCI (2012)
- LBDs are now included in DSM V (2013)
- Neurocognitive disorder with Lewy bodies
- Neurocognitive disorder due to Parkinson’s disease
Topic 3 - Lewy Body Dementias (LBD): Dementia with Lewy Bodies (DLB) and Parkinson’s Disease Dementia (PDD)

Establish symptomatic trials

Set up clinical cohort studies from prodrome to autopsy

Use existing cohorts and bio-resources to discover mechanisms using brain mapping and identifying rare genetic variants

Improve imaging and other biomarkers both for diagnosis and disease progression

Develop new animal, cellular, and in vitro models to identify strategies that can be carried forward into clinical trials
Six trials met the inclusion criteria for this review, in which a total of 1236 participants were randomised.

Four of the trials were of a parallel group design and two cross-over trials were included. Four of the trials included participants with a diagnosis of Parkinson's disease with dementia (Aarsland 2002a; Dubois 2007; Emre 2004; Ravina 2005), of which Dubois 2007 remains unpublished. Leroi 2004 included patients with cognitive impairment and Parkinson's disease (both with and without dementia).

Patients with dementia with Lewy bodies (DLB) were included in only one of the trials (McKeith 2000).

One further DLB trial published since this review – Mori 2012
Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease (March 2012)

For global assessment, three trials comparing cholinesterase inhibitor treatment to placebo in PDD reported a difference in the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) score of -0.38, favouring the cholinesterase inhibitors (95% CI -0.56 to -0.24, P < 0.0001).

For cognitive function, a pooled estimate of the effect was consistent with the presence of a therapeutic benefit (standardised mean difference (SMD) -0.34, 95% CI -0.46 to -0.23, P < 0.00001). There was evidence of a positive effect of cholinesterase inhibitors on the Mini-Mental State Examination (MMSE) in patients with PDD (WMD 1.09, 95% CI 0.45 to 1.73, P = 0.0008) and in the single PDD and CIND-PD trial (WMD 1.05, 95% CI 0.42 to 1.68, P = 0.01) but not in the single DLB trial.

For behavioural disturbance, analysis of the pooled continuous data relating to behavioural disturbance rating scales favoured treatment with cholinesterase inhibitors (SMD -0.20, 95% CI -0.36 to -0.04, P = 0.01).

For activities of daily living, combined data for the ADCS and the Unified Parkinson's Disease Rating Scale (UPDRS) activities of daily living rating scales favoured treatment with cholinesterase inhibitors (SMD -0.20, 95% CI -0.38 to -0.02, P = 0.03).
Donepezil for cognitive impairment in Parkinson’s disease: a randomised controlled study


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<tr>
<td>Male/Female</td>
<td>13/1</td>
</tr>
<tr>
<td>Age</td>
<td>71 (±3.9)</td>
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<tr>
<td>Duration PD (yrs)</td>
<td>10.8 (±5.2)</td>
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<tr>
<td>Duration Cog Imp.</td>
<td>3.0 (±2.6)</td>
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<tr>
<td>MMSE</td>
<td>20.8 (±3.4)</td>
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<tr>
<td>Hoehn &amp; Yahr</td>
<td>2.4 (1-4)</td>
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<tr>
<td>L-Dopa dose (mg/d)</td>
<td>485 (±256)</td>
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![Graph showing MMSE scores over time for different groups](image)

General linear model: p=0.013
PD EXPRESS study – rivastigmine in PDD
(Emre et al, New Eng J Med 2004)

Change from baseline ADAS-cog

a) Hallucinators

* \( p = 0.002 \) vs placebo

b) Non-hallucinators

* \( p = 0.015 \) vs placebo

Visual hallucinators; \( n = 107 \) and 60 rivastigmine- and placebo-treated patients
Non-visual hallucinators; \( n = 220 \) and 101 rivastigmine- and placebo-treated patients
COGDRAS Speed of Attention

Hallucinations predict treatment response in DLB

Cholinesterase inhibitors in Dementia with Lewy Bodies – which one to use?

Mani Bhasin, Elise Rowan, Keith Edwards, Ian McKeith (Int J Ger Psych 2007 890-895)
63 patients with DLB or PDD randomised to 5mg memantine or placebo

Increased to 10mg bd by week 4

CHEIs allowed

24 weeks treatment

Blinded rater at weeks 0, 12 and 24
Primary Outcome was CGIC – P=0.03 (MWU)
PDD 4.3 vs DLB 2.9 (n.s.)
27% improved on drug
0% improved on placebo

1.9 point difference in MMSE (greater than CHEIs)

No change in UPDRS or NPI

20% dropouts on drug and 23% placebo – no consistent pattern, no increased confusion on drug.
199 patients with DLB or PDD randomised to memantine 20mg once daily or placebo. Included titration phase.

No CHEIs, no psychotropics initiated during study.

No primary outcome specified

80% completed 24 weeks of treatment

Stroke, falls and worsening dementia were most common SAEs

Dropouts equally common in active (11%) and placebo (12%) groups
Memantine for patients with Parkinson’s disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial

Small improvements in CGIC and NPI (delusions, hallucinations, eating and sleeping) in DLB group after 24 weeks but no change in PDD.

Cognitive test scores did not consistently improve in either treatment group, and the groups did not differ significantly in activities of daily living scores, motor symptoms, or caregiver burden.
Combined memantine/DLB treatment in Aarsland et al, 2009

At 78 years

CT: Normal. MMSE 25/30

After 2 years treatment with rivastigmine alone:
MMSE 21/30, wheelchair, 24h nursinghome.

After 9 months treatment:
with rivastigmine and memantine
MMSE 26/30

Courtesy of Dr Elisabet Londos
Malmö Skåne University Hospital Sweden
Challenges for DLB/ PDD trials – what have we learned so far?

• Response heterogeneity
  – We should not pool DLB and PDD patients?
  – We should look for responders using case studies and adaptive designs

• We probably need to use multiple as well as single agents
Challenges for DLB/ PDD trials – the future

• Clinical outcome measures need to be better developed for this population

• Diagnostic biomarker changes need to be correlated with disease severity / progression
Alzheimers

MMSE 20/30
Orientation 5/10
Short term memory 0/3

DLB / PDD

MMSE 20/30
Orientation 8/10
Short term memory 2/3
Alzheimers

- MMSE 20/30
- Orientation 5/10
- Short term memory 0/3

DLB / PDD

- MMSE 20/30
- Orientation 8/10
- Short term memory 2/3

- MoCA
- DRS-2
- SCOPA-COG
- PD-CRS
LBD biomarkers have so far been developed for diagnosis, not progression.
Fifteen subjects (12 male, median age 74 years, range 67-84 years) were given 250mg armodafanil in the morning.

Thirteen had baseline and 3 month data on the Maintenance of Wakefulness Test (MWT) - 11 subjects improved (median value 11 minutes, range 1-22).

Improvement on the Epworth Sleepiness Scale occurred in 14 subjects (median 6 points, range 1-15).

MMSE scores were relatively stable (1/-4 points) compared to baseline except for a 6 point improvement in 1 subject.

Scores improved on the NPI-VH in 6 and on the NPI-A in 10.

QOL was rated as improved in 7 subjects and in 7 caregivers.
Challenges for DLB trials – feasibility issues

• Robust and well accepted clinical diagnostic criteria exist for LBDs but DLB in particular is seen as a high risk trial population
  
  – hard to recruit – AD investigator sites not generally suitable but no DLB trial network established yet
  – potentially sensitive to adverse events
  – inherent fluctuation makes measurement difficult
  – uncertain regulatory acceptance
  – placebo trials ethical but difficult in practice