Diagnosis and Management of Lewy body dementias

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Columbia University

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Learning Objectives

1. Recognize the clinical and pathological characteristics of Lewy body dementias, and how they differ from Alzheimer’s disease

2. Become familiar with imaging and fluid biomarkers and their role in diagnosis of Lewy body dementias

3. Learn management strategies for motor, cognitive and psychiatric aspects of Dementia with Lewy bodies and Parkinson’s disease dementia
PDD and DLB have more similarities than differences

- ‘Lewy body disease’ is an umbrella term for studying biology of PD, PDD and DLB
- Common pathobiology related to misfolding and toxic aggregation of α-synuclein – ‘Lewy Body Disorders’
- For clinical care and clinical research, the distinction between those with primary symptom complex of dementia (DLB) and those with a primary movement disorder is important (PDD), and the ‘one year rule’ should be used.

DLB/PDD Working Group Neurology 2007
Lewy Body Dementias

- Parkinson’s Disease
  - Mild Cognitive Impairment
  - PD Dementia
  - Dementia with Lewy Bodies (DLB)
**DLB and PDD**

Lewy Body Disorders (synucleinopathies)

- Main difference is the timing of onset of dementia in relation to motor symptoms

- For clinical research: *one year rule*
  - Patients have **DLB** when dementia is early and predominant
  - Patients have **PDD** when they develop cognitive impairment in the context of otherwise typical PD
Overlapping clinicopathologic syndromes

**AD**: Neuritic type senile plaques (SP) and neurofibrillary tangles (NFT)

**PD**: Lewy bodies in substantia nigra → nigrostriatal DA loss

**DLB and PDD**: Cortical Lewy bodies & Lewy neurites; Diffuse type SP; fewer NFT

**PD**: Lewy bodies in substantia nigra → nigrostriatal DA loss

**DLB and PDD**: Cortical Lewy bodies & Lewy neurites; Diffuse type SP; fewer NFT
Lewy body

Cytoplasmic inclusion, round, 8 - 30 µm

Brainstem type, discrete
Cortical type, ill-defined

Found in

5% of asymptomatic, elderly subjects
100% of patients with Parkinson disease
or with Lewy body dementia
Neuronal loss
Cytoplasmic inclusion: Lewy body

- Dorsal nucleus of vagus
- Nucleus coeruleus
- Pars compacta of substantia nigra
- Hypothalamus
- Substantia innominata -> Mesolimbic cortex

If, in addition,
neurons with Lewy body in
cerebral neocortex (-> dementia)

If, in addition,
neuritic plaques or neurofibrillary tangles or
both in cerebral cortex
(as seen in Alzheimer disease)

- Parkinson disease
- Diffuse Lewy body disease
- Alzheimer Disease
- Lewy body variant
Cellular Pathology of DLB and PDD: Common features

- There are no hallmark neuropathologic features that distinguish DLB and PDD
- Cortical Lewy bodies are widespread in both DLB and PDD and correlate with severity of dementia (Hurtig 2000, Aarsland 2005)
- Structure of Lewy bodies, composed principally of alpha synuclein aggregates, is identical in PD, PDD and DLB.
- Other pathologic substrates of DLB and PDD: neuronal loss, basal forebrain cholinergic degeneration, AD, and vascular pathology
Genetics of PDD and DLB

Meeus Arch Neurol 2012
MDS Clinical Diagnostic Criteria for Dementia associated with PD—Core Features

- Queens Square Diagnostic criteria for PD
- Insidious, slowly progressive
- Impairment in more than one cognitive domain
- Decline from premorbid level
- Severe enough to impair social, occupational, or personal care independent of motor function

Emre et al Mov Disord 2007
Neuropsychological Profile of PDD

Impairment in:

- **Executive** function (planning, initiating, sequencing, monitoring, shifting between responses)-Trails A-B, verbal fluency
- **Memory**: Impaired free recall of verbal and nonverbal memory with *preserved* recognition.
- **Visuospatial** skills: both perception and construction such as copying cube and judgment of line orientation
- **Attention** with fluctuations-digit span, serial 7s
## Movement Disorders Society Criteria for Probable PDD

<table>
<thead>
<tr>
<th>Core Features</th>
<th>Associated Features</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable PDD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. PD diagnosis</td>
<td>1. Cognitive deficits in two of four domains (attention, executive function, visuospatial function, and free recall)</td>
<td>1. Vascular disease on imaging or other abnormality that may cause cognitive impairment, but not dementia</td>
</tr>
<tr>
<td>2. Slowly progressive dementia</td>
<td>2. At least one behavioral symptom (apathy, depression/anxiety, hallucinations, delusions, or excessive daytime sleepiness)</td>
<td>2. Unknown time interval between motor and cognitive symptoms</td>
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<tr>
<td></td>
<td></td>
<td>3. Acute confusion resulting from systemic diseases or abnormalities or drug intoxication</td>
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<td></td>
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<td>4. Features compatible with probable vascular dementia</td>
</tr>
</tbody>
</table>
Prevalence and Incidence of PDD

- 12 studies of PD/PDD (1767 patients) (Aarsland 2005)
  - Prevalence of dementia = 24.5% (17.4-31.5)
- 4 studies of PDD
  - Prevalence of dementia = 31.1% (20-42.1)
- Estimated prevalence of PDD in general population >65 is 0.5%
- Among all patients with dementia, 3.6% are associated with Parkinson’s Disease
- Among cohorts followed longitudinally 50% will develop dementia over 10 years, 83% at 20 years (Hely 2008)
Risk Factors for Dementia in PD

- Age, not age at onset of PD
- Severity of extrapyramidal signs
- Postural Instability Gait Disorder (PIGD), not tremor-dominant PD
- Male gender
- Family history of dementia
- Depression
- Low education
- Mild Cognitive Impairment (MCI)
The spectrum of cognitive impairment in Lewy body diseases

Potential modifiers that may contribute to progression, stability, or reversion across PD cognitive categories:

- Demographic
- Biological: susceptibility genes, environmental factors, neuropathology
- Clinical: neuropsychological patterns or PD-MCI subtypes, cognitive test performance, other behavioral features (depression, apathy, sleepiness, etc), medications for motor, cognition, or other non-motor symptoms

Movement Disorders
# Comparison of PD PDD and AD

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>PD Dementia</th>
<th>AD</th>
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</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
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<tr>
<td>Immediate Free Recall</td>
<td>Mildly Impaired</td>
<td>Impaired</td>
<td>Impaired</td>
</tr>
<tr>
<td>Delayed Free Recall</td>
<td>Mildly Impaired</td>
<td>Impaired</td>
<td>Severely Impaired</td>
</tr>
<tr>
<td>Delayed Recognition</td>
<td>Normal</td>
<td>Normal</td>
<td>Severely Impaired</td>
</tr>
<tr>
<td>Percent Retention</td>
<td>Normal (&gt;70 %)</td>
<td>Nl.–Mild Impaired (&gt;50 %)</td>
<td>Severely Impaired (&lt;50%)</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naming</td>
<td>Normal Impaired</td>
<td>Normal – Mildly impaired</td>
<td>Severely Impaired</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>Impaired</td>
<td>Severely Impaired</td>
<td>Impaired</td>
</tr>
<tr>
<td><strong>Orientation</strong></td>
<td>Normal</td>
<td>Normal or Impaired</td>
<td>Impaired</td>
</tr>
<tr>
<td><strong>Visuospatial Skills</strong></td>
<td>Impaired</td>
<td>Impaired</td>
<td>Impaired</td>
</tr>
<tr>
<td><strong>Executive Function</strong></td>
<td>Impaired</td>
<td>Severely Impaired</td>
<td>Severely Impaired</td>
</tr>
</tbody>
</table>
### Montreal Cognitive Assessment (MoCA)

**Executive Function**: 0/2

**Visuospatial**: 0/3

**Naming**: 3/3

**Memory**: 4/5

**Attention**: 6/6

**Language**: 3/3

**Abstraction**: 2/2

**Orientation**: 6/6

**Total**: 24/30
Diagnostic Criteria for DLB
McKeith et al, Neurology, 2005

• Cognitive decline & reduced social/occupational function
  • Attentional, executive and visuospatial dysfunction prominent

• CORE features
  • Fluctuation
  • Recurrent visual hallucinations
  • Spontaneous parkinsonism

• Suggestive features
  • REM sleep behavior 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

Clinical diagnosis is to be incorporated into DSM V
Consensus Guidelines for Dementia with Lewy Bodies

Central Feature:
Progressive cognitive decline that interferes with social/occupational function
Memory impairment may not occur in the early stages, but is usually evident with progression
Prominent impairment in attention, executive function, visuospatial skills

McKeith et al. Neurology 2005
Consensus Guidelines for Dementia with Lewy Bodies

Two of the following core features are sufficient for probable DLB, and one is sufficient for possible DLB

* Fluctuating cognition with pronounced variation in attention and alertness (75% of all dementia)
* Recurrent visual hallucinations that are well formed and detailed (70% of DLB early and persistent)
* Spontaneous features of parkinsonism (10-78%, PIGD form)

Suggestive features: (if one or more in the presence of 1 or more core features - probable DLB. If one or more alone, possible DLB)

- REM sleep behavior disorder, severe neuroleptic sensitivity, low dopamine transporter uptake in basal ganglia by SPECT or PET imaging
Consensus Guidelines for Dementia with Lewy Bodies

Features supportive of diagnosis
a. Repeated falls
b. Syncope
c. Transient loss of consciousness
d. Severe autonomic dysfunction
e. Systematic delusions
f. Hallucinations in other modalities
g. Depression
h. Relative preservation of medial temporal lobe structures on CT/MRI
i. Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
j. Abnormal MIBG myocardial scintigraphy
k. Prominent slow wave activity on EEG with temporal lobe transient sharp waves.
Epidemiology of DLB

- Prevalence estimates (6 studies) range from 0-5% of general population, and from 0-30.5% of all dementia cases (Zaccai 2005)
- Incidence is 0.1% annually in general population, and 3.2% a year among all incident dementia cases (Zaccai 2005)
- No reported differences in ethnic or gender distribution
- Diagnostic accuracy is low (sensitivity 34%-65%)
Vignette: DLB

- 64 year old man with a 2 year history of progressive memory impairment followed by noticeable word finding difficulty. Simple routine tasks required more time such as finding the door handle in his car, or paying bills. At the same time his walking slowed down, and his voice was softer. Six months before diagnosis, he had his first visual illusions. At presentation he had signs of parkinsonism including bradykinesia, rigidity and rest tremor.
Neuropsychological testing

• Impaired acquisition and retrieval of both verbal and non-verbal information with deficient retention.

• Poor attention

• Poor visuospatial skills

• Normal language
“I came home one day and found my daughter (who lives in California) asleep on the living room couch. I was startled to see her because we were not expecting a visit. As I approached the couch, my daughter turned into a small pile of coats and throw cushions. It was somewhat disconcerting, but like “Harvey”, the six foot rabbit from the Broadway theater, I found the experience more funny than ominous. As time progressed, each of my children appeared singly, in pairs, or in groups of three. They were non-vocal, frequently appeared to be sleeping, and did not relate to me or to each other.”

January 14, 1997, note to his doctor.
Clinical Course

• As illness progressed he lost awareness of fictitious nature of illusions and hallucinations and became paranoid
• Treated with risperidone, olanzapine and clozapine
• Developed orthostatic blood pressure changes
• Depression treated with sertraline
• Swallowing difficulty and aspiration
New Cognitive Assessment Tools

• **MMSE** has been used as cognitive screen for dementia with 41% ≤ 25 and 18.5% scoring ≤ 24 (Sutcliffe 1992)

• **SCOPA Cog** (Marinus 2003, Verbaan et al 2007)
  – 58% scored below cutoffs on SCOPA Cog, but not MMSE (lowest quartile)
  – Most prominent impairment: executive, memory
  – 22% had impaired cognition compared to controls

• **CAMCOG R** (Athey 2005)
  – 15/94 who scored <25 on MMSE scored below cutoffs

• **Montreal Cognitive Assessment (MOCA)** (Nasreddine 2005)

• **PANDA** (Kalbe 2007)

• *Poor performance on each associated with age, duration of PD, severity of EPS, PIGD motor subtype.*
Improving Clinical Detection of Lewy Body Dementia with The Lewy Body Composite Risk Score

Table 1
Lewy body composite risk score

<table>
<thead>
<tr>
<th>Physical Findings</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>Have slowness in initiating and maintaining movement or have frequent hesitations</td>
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<tr>
<td>or pauses during movement?</td>
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<tr>
<td>Have rigidity (with or without cogwheeling) on passive range of motion in any of</td>
<td></td>
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<tr>
<td>the 4 extremities?</td>
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<tr>
<td>Have a loss of postural stability (balance) with or without frequent falls?</td>
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<td></td>
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<tr>
<td>Have a tremor at rest in any of the 4 extremities or head?</td>
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<td></td>
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<tr>
<td>Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?</td>
<td></td>
<td></td>
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<tr>
<td>Have episodes of illogical thinking or incoherent, random thoughts?</td>
<td></td>
<td></td>
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<tr>
<td>Have frequent staring spells or periods of blank looks?</td>
<td></td>
<td></td>
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<tr>
<td>Have visual hallucinations (see things not really there)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appear to act out his/her dreams (kick, punch, thrash, shout or scream)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have orthostatic hypotension or other signs of autonomic insufficiency?</td>
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<tr>
<td>Total score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean LBCRS scores

- **DLB** 6.1 (2.0) vs **AD** 2.4 (1.3).

- Using a cutoff score of 3, ROC for DLB vs. AD 0.93 (0.89-0.98)

- MCI-DLB vs. MCI-AD ROC 0.96 (0.91-1.0)

- LBCRS may identify LB pathology as contributor to dementia

Galvin. Alz Dem (2015) 316-324
Clinical diagnostic accuracy was 80% (fluctuations 80%, parkinsonism 77%, hallucinations 70%).

Lower frequency of core features associated with decreasing LB distribution and increasing neuritic plaques.
Probability that the pathologic findings are associated with a DLB clinical phenotype

<table>
<thead>
<tr>
<th>Lewy body type pathology</th>
<th>NIA Reagan Low (Braak 0-II)</th>
<th>NIA Reagan Interm. (Braak III-IV)</th>
<th>NIA Reagan High (Braak V-VI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Limbic (transitional)</td>
<td>High</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>Diffuse neocortical</td>
<td>High</td>
<td>High</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

Distinguishing DLB and AD

• Concomitant AD tangle pathology (Braak III-VI) is associated with decreased hallucinations and lower diagnostic accuracy 39% compared to 75% (Merdes 2003).

• Best model for early diagnosis of DLB (n=23) compared to AD (n=94) included presence of hallucinations (PPV 84%) and absence of visuospatial impairment (NPV 90%) (Tiraboschi 2006)
Prospective Studies of Effect of ApoE4 on Cognitive decline in PD

- Longitudinal follow-up of 528 PD, 512 controls for 5 years from diagnosis revealed no significant impact of ApoE4 on risk of dementia or rate of cognitive decline. (Williams Gray 2009).
- In the CamPaIGN study, No effect of ApoE4 on cognitive decline. (Williams Gray 2009).
  - COMT genotype was not related to decline; MAPT H1/H1 was associated with posterior cortical cognitive impairment.
  - Suggests two distinct cognitive syndromes: Frontostriatal versus posterior cortical
- ApoE4 was associated with cognitive decline in 114 PD pairs (cognitive decliners vs. non-decliners) over 3 years (Ma 2011)
ApoE4 and Cognitive decline in PD

- Mattis DRS declined 3 points per year faster among E4 carriers with PD.
- ApoE associated with decline in initiation, construction, memory
- MAPT H1/H1 lower scores in memory throughout
- COMT Met/Met higher attention scores throughout

HR 2.8 increased risk of > 10 pt decline

Estimated Association With Annual Change in DRS-2

<table>
<thead>
<tr>
<th></th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE ε4^+a</td>
<td>-2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ε2^+a</td>
<td>0.94</td>
<td>0.24</td>
</tr>
<tr>
<td>MAPT H1/H1^b</td>
<td>-0.63</td>
<td>0.29</td>
</tr>
<tr>
<td>COMT Met/Met^c</td>
<td>0.1</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Morley J, Mov Disord 2012
Clinical and neuropathological similarities between dementia with Lewy bodies (DLB), Parkinson's and Alzheimer's diseases (PD and AD, respectively) suggest that these disorders may share etiology. To test this hypothesis, we have performed an association study of 54 genomic regions, previously implicated in PD or AD, in a large cohort of DLB cases and controls. The cohort comprised 788 DLB cases and 2624 controls. To minimize the issue of potential misdiagnosis, we have also performed the analysis including only neuropathologically proven DLB cases (667 cases). The results show that the APOE is a strong genetic risk factor for DLB, confirming previous findings, and that the SNCA and SCARB2 loci are also associated after a study-wise Bonferroni correction, although these have a different association profile than the associations reported for the same loci in PD. We have previously shown that the p.N370S variant in GBA is associated with DLB, which, together with the findings at the SCARB2 locus, suggests a role for lysosomal dysfunction in this disease. These results indicate that DLB has a unique genetic risk profile when compared with the two most common neurodegenerative diseases and that the lysosome may play an important role in the etiology of this disorder. We make all these data available.
Glucocerebrosidase and PD

- Two mutations in glucocerebrosidase (GBA) causes Gaucher disease.
- A single mutation may be the most common genetic susceptibility for PD.
- Nearly 20% of all Ashkenazi Jews with PD carry a mutation in GBA (Clark 2009).
- PD patients are 5.4 fold more likely to carry GBA mutations than controls (Sidransky 2009). The risk for PD in carriers is unknown.
GBA mutation carriers were significantly more likely to have cortical LB (28/34 = 82.3%) than were non-mutation carriers (66/153 = 43.1%; p<0.001).

The presence of a GBA mutation appeared to relate more to cortical LB, than to LB confined to subcortical regions (IPD).

Non-mutation carriers were more likely to meet NIA RI criteria for AD and were more likely to have an ApoE4

Clark et al, Arch Neurol 2009
Multicenter analysis of GBA in DLB
Sidransky et al. (2012)

GBA genotypes from 11 centers
721 cases with DLB, 1962 controls.
450 cases were autopsied, 80% of cases had full GBA sequencing
Odds ratio = 8.28 (95%CI = 4.78 – 14.88).

Age at diagnosis ~ 5 years earlier in GBA carriers with DLB.
Mutations associated with severity (H&Y, UDPRS).
Mutations in GBA play an even larger role in DLB than PD.

GBA mutations increase risk for LBD with and without AD Path - Tsuang (2012)

GBA mutations present in 7.6% pDLB, 3.6% of LBD-AD, 0.8% of AD and 0.8% controls

Odds Ratio pLBD v. Controls 7.6 (1.8-31.9)
LBD-AD v. Controls 4.6 (1.2-17.6)
AD v. Controls 1.1 (0.2- 6.6)
Biomarkers

- Biomarkers are quantitative measures of dynamic processes that reflect ongoing disease.
  - Detecting disease during premanifest state-important for early intervention
  - Diagnosis- guiding participant selection for clinical trials (reduced variance, smaller sample size)
  - Quantification of disease progression-reduce time to primary outcome in a clinical trial
Neuroimaging

- **SPECT**
  - $^{99}\text{mTc}}$-HMPAO to differentiate DLB and AD based on occipital perfusion
  - $^{123}\text{I}}$-FP-CIT to examine striatal dopamine transporter loss

- **PET**
  - $^{18}\text{F}}$ FDG PET to examine cerebral glucose metabolism
  - Fluorodopa PET to assess striatal dopamine
  - AChE activity –cholinergic activity
  - Amyloid imaging-PIB, $^{18}\text{FBAY94-9172}$, $^{18}\text{AV-45}$

- **MRI**
Striatal dopamine loss is a clinically useful biomarker for DLB.

Phase III study: 77.7% sensitivity, 90.4% specificity (McKeith 2007).

Intl Consensus Criteria, NICE, EFNS recommend to differentiate DLB and AD.
DAT imaging with $^{123}$I Beta CIT and SPECT

<table>
<thead>
<tr>
<th></th>
<th>Number of Subjects</th>
<th>Outcome Rate (%)</th>
<th>P Value for Trend</th>
<th>ORs (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1</td>
</tr>
<tr>
<td>MMSE &lt; 24</td>
<td>491</td>
<td>19 (3.9)</td>
<td>0.0293</td>
<td>7.6 (0.8, 68.4)</td>
</tr>
<tr>
<td>MoCA &lt; 26</td>
<td>489</td>
<td>137 (28.0)</td>
<td>0.0002</td>
<td>3.3 (1.7, 6.7)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>491</td>
<td>34 (6.9)</td>
<td>0.0002</td>
<td>12.9 (2.6, 62.4)</td>
</tr>
<tr>
<td>GDS $\geq$ 5</td>
<td>490</td>
<td>97 (19.8)</td>
<td>0.0056</td>
<td>2.8 (1.3, 5.7)</td>
</tr>
<tr>
<td>Postural instability</td>
<td>488</td>
<td>37 (7.6)</td>
<td>0.0018</td>
<td>4.9 (1.6, 15.2)</td>
</tr>
<tr>
<td>Falling</td>
<td>490</td>
<td>60 (12.2)</td>
<td>0.0089</td>
<td>2.2 (0.9, 5.1)</td>
</tr>
<tr>
<td>QoL decline</td>
<td>489</td>
<td>122 (25.0)</td>
<td>0.0537</td>
<td>1.8 (0.9, 3.4)</td>
</tr>
<tr>
<td>S/E ADL decline $\geq$ 15</td>
<td>490</td>
<td>67 (13.7)</td>
<td>0.0066</td>
<td>2.8 (1.2, 6.3)</td>
</tr>
</tbody>
</table>

- 491 PD cases, duration 2.06 (1.38) years, MMSE 29.3
- Followed 5.5 years
- Subjects in the bottom quartile for striatal binding, compared to the top quartile, had an odds ratio 3.3 (1.7, 6.7) for cognitive impairment.
- Change from baseline in imaging after 22 months was also independently associated with motor, cognitive, and behavioral outcomes.

Ravina Mov Disord. 2012
Cerebral metabolic reduction (PET) in comparison to age-similar normal controls in autopsy-confirmed cases. On the medial views (RT.MED and LT.MED), there is sparing of glucose metabolism in the occipital cortex in AD (arrows), but significant reduction is seen in DLB, LBVAD, and DLBD.

Minoshima et al. 2001; Annals of Neurology
<table>
<thead>
<tr>
<th></th>
<th>Dementia with Lewy Bodies</th>
<th>Alzheimer’s Disease</th>
<th>Parkinson’s Disease Dementia</th>
<th>Other Lewy body disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>123I-FP SPECT</td>
<td></td>
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<td>Abnormal in PSP, CBD, MSA</td>
</tr>
<tr>
<td>(McKeith 2007)</td>
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<tr>
<td>(Walker 2007), O’Brien (2009)</td>
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<tr>
<td>18F FDG PET,</td>
<td>Med. Occip</td>
<td>Pariet Temp</td>
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<tr>
<td>99 Tc HMPAO SPECT</td>
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<tr>
<td>AchE PET</td>
<td>Med. Occip</td>
<td>Temp</td>
<td>Med. Occip</td>
<td>Cortical AchE more extensive in DLB, PDD than AD</td>
</tr>
<tr>
<td>Bohnen 2003</td>
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<tr>
<td>Shimada 2009</td>
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<tr>
<td>Amyloid Imaging</td>
<td></td>
<td></td>
<td></td>
<td>PDD, PD and controls similar</td>
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<td>PIB</td>
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<td>Gomperts 2008</td>
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<td>Edison 2008</td>
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<tr>
<td>Structural MRI</td>
<td>Preservation Med temporal</td>
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<td>Preservation Med temporal</td>
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<td>Whitwell 2007</td>
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</table>
# Biomarkers in AD, DLB, PD(D)

Table 1 Summary of neuropathologic, clinical, imaging and fluid markers in dementia with Lewy bodies, Parkinson’s disease and Alzheimer’s disease

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>AD and DLB</th>
<th>DLB</th>
<th>DLB and PD(D)</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropathology</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Neurofibrillary tangles</td>
<td>Amyloid plaques</td>
<td></td>
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<tr>
<td><strong>Clinical symptoms</strong></td>
<td>Cognitive decline</td>
<td>Spontaneous hallucinations</td>
<td>Cognitive decline</td>
<td>RBD</td>
<td>L-Dopa response</td>
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<tr>
<td><strong>Nuclear imaging</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PIB binding↑</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>CSF biomarkers</strong></td>
<td>tau↑</td>
<td>β-Amyloid 1-42↓</td>
<td>β-Amyloid 1-40ox↑</td>
<td>α-Synuclein↓</td>
<td>α-Synuclein↓</td>
</tr>
<tr>
<td></td>
<td>p-tau↑</td>
<td>Soluble NG2↓</td>
<td>CART↓</td>
<td>Neurosin↓</td>
<td>Oligomeric α-synuclein↑</td>
</tr>
<tr>
<td><strong>Serum biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>H-FABP↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ca/Mg↑</td>
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</tbody>
</table>

AD, Alzheimer’s disease; CART, cocaine and amphetamine regulated transcript; CSF, cerebrospinal fluid; DAT, dopamine transporter imaging; DLB, dementia with Lewy bodies; H-FABP, heart-type fatty acid binding protein; NF, neurofilament; NG2, Neuron glia 2; PD, Parkinson’s disease; PDD, Parkinson’s disease with dementia; PIB, Pittsburgh compound B; p-tau, phosphorylated tau protein; RBD, REM sleep behaviour disorder.

Schade and Mollenhauer *Alzheimer’s Research & Therapy* 2014, 6:72
CSF A Beta \(_{1-42}\)

- Substantial agreement that low A Beta\(_{1-42}\) is found in both PDD and DLB and may be correlated with cognitive impairment (Mollenhauer 2006, Compta 2009, Maetzler 2009).

- 19% reduction of A Beta\(_{1-42}\) in newly diagnosed PD compared to controls in ParkWest and correlation with memory performance. No correlation with Tau (Alves 2010).

- Low A Beta\(_{1-42}\) independent predictor of cognitive decline (Siderowf 2010).

- Low A Beta\(_{1-42}\) predicts MCI in incident PD cohort (PPMI) after 2 years (Teralonge 2015)

- A Beta\(_{1-42}\) does not distinguish between DLB and AD (Gomez Tortosa 2003, Mollenhauer 2005)
Reduced CSF A\textbeta_{1-42} independent predictor of cognitive decline in PD

CSF level of $\leq 192$ associated with a decline of 5.85 points/year on Mattis Dementia Rating Scale

CSF tau or p-Tau not associated with decline

Siderowf, Neurology 2010
Biomarkers to distinguish AD and LBD

**Alzheimer Pathology**
- ApoE, PS1
- Amyloid imaging
- FDG PET
- ↓ A Beta 1-42
- ↑ T-tau, P Tau

**Alpha Synuclein Pathology**
- GBA, DJ1, SNCA, MAPT H1/H1 haplotype
- DAT imaging
- ↓ Alpha synuclein
- ↑ NF-L (disease severity)
- Cardiac MIBG
- Serum/CSF urate
- Plasma EGF
COMBINING BIOMARKERS DISTINGUISHING DLB/PDD from AD

- GBA mutation: present
- APOE4: ? less frequent or present
- CSF Aβ42: low
- CSF t-tau: normal or slightly high
- CSF α-synuclein: low
- DAT imaging: positive
Spectrum of Lewy Body Disorders

- PD
- PDD
- LBvAD
- CSF Alpha Synuclein
- CSF A Beta 1-42
- GBA (Alpha synuclein)
- ApoE4 (A Beta 1-42)
- T-Tau
- P-Tau
- DLB+
- AD ch
- LBvAD

Cognitive impairment
Treatment of Cognitive Impairment in PDD and DLB

- Like AD, cholinesterase inhibitors are the mainstay of symptomatic treatment
- Rivastigmine up to 12mg oral or 9.5 mg/24 hour patch has been used in RCT of PDD (Emre 2004) and DLB (McKeith 2000)
- Open label rivastigmine 76 weeks (PDD) significant efficacy (Poewe 2006, Emre 2014)
- 2 RCT of donepezil (Aarsland 2002, Ravina 2005) in PDD.
- RCT of donepezil in DLB (Ikeda 2015, Mori 2015)
- Memantine in PDD (Aarsland 2009, Subendorff 2014)
• Improvement in neuropsych test performance, ADL, NPI, clock drawing, CDR power of attention, verbal fluency
• Magnitude of the effect on global ratings of cognition, in particular attention and executive function, was comparable to that seen in AD
• Adverse effects: Nausea, vomiting, worsening tremor in 10%.
Ongoing trials

- SYNAPSE: phase II study of safety, tolerability and efficacy of SYN20, a dual 5-HT6/5-HT2A antagonist (NCT02258152)
- PD-MCI Dopaminergic system- rasagiline
- PD-MCI Noradrenergic system- atomoxetine
Non-Pharmacologic RX

- Cognitive therapies-speed of processing
- Physical exercise (skill based, aerobic, social contact)
- rTMS (noninvasive brain stimulation)
Treatment of Parkinsonism

- Up to 78% of DLB cases have an extrapyramidal syndrome.
- Levodopa (mean dose 323 mg) is effective in approximately 1/3 of DLB cases (36% DLB, 70% PDD, 57% PD). Younger DLB cases more responsive (Molloy 2006).
- Physical therapy
Management of Psychosis

• Reduce anticholinergic medications.
• Simplify PD regimen (MAO-B inhibitors, amantadine, dopamine agonists, COMT inhibitors, then levodopa.
• Benzodiazepines should be avoided (except in the case of RBD)
• Cholinesterase inhibitors (rivastigmine may be effective)
• Among antipsychotics, only clozapine has established utility for PDD (level 1).
• Quetiapine is most commonly used atypical antipsychotic in clinical practice.
• Pimavanserin 40 mg(highly selective 5HT2A inverse agonist) was effective in 6 week RCT in 90 patients with PD compared to 90 placebo
# Treatment of Depression and Psychosis in Lewy Body Disorders

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Starting dose</th>
<th>Max dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>sertraline</td>
<td>25</td>
<td>100-200</td>
</tr>
<tr>
<td></td>
<td>paroxetine</td>
<td>10</td>
<td>20-40</td>
</tr>
<tr>
<td></td>
<td>citalopram</td>
<td>10</td>
<td>20-40</td>
</tr>
<tr>
<td>Atypical Antipsychotic</td>
<td>quetiapine</td>
<td>12.5 mg HS</td>
<td>100-200</td>
</tr>
<tr>
<td></td>
<td>clozapine</td>
<td>6.25 q day</td>
<td>50 mg</td>
</tr>
<tr>
<td></td>
<td>olanzapine</td>
<td>2.5</td>
<td>5-10</td>
</tr>
<tr>
<td></td>
<td>risperidone</td>
<td>.25 mg HS</td>
<td>2 mg</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Clonezepam</td>
<td>.25 mg HS</td>
<td>.25-1.5</td>
</tr>
</tbody>
</table>

*FDA warning exists due to data suggesting increased risk for cerebrovascular events and higher mortality.
Neuroleptic Sensitivity

• Severe neuroleptic sensitivity is associated with DLB 53%, PDD 39% and PD 27%, but not with AD (Aarsland 2005)
• Neuroleptics may have adverse disease modifying effects and be associated with increased tangle burden in DLB patients exposed to these agents (Ballard 2005)
Sleep Disorders and other Non-Motor Symptoms

• Sleep disorders include: sleep fragmentation, nightmares, and REM Behavior disorder.
• Transdermal rotigotine patch for fragmented sleep (Trenkwalder 2011)
• Clonazepam or melatonin for RBD
• Modafinil and caffeine for excessive daytime sleepiness
• Other non-motor symptoms: apathy, postural hypotension, hyperactive bladder, GI symptoms, pain
What do we need to know about DLB?

- How to diagnose it better and earlier
- Clinical diagnosis alone is unlikely to be adequate – need biomarker profiling
- We particularly need to understand
  - the prodromal syndrome and the factors influencing risk and progression of DLB
  - how to use existing agents for optimal symptomatic treatment
- We need better outcome measures
- We need to know how to optimally organize care pathways for DLB