Welcome to the Webinar!

The program will begin momentarily

Please use the chat function to ask questions
Research and Clinical Development in Lewy Body Dementia
Thank You ACT-AD Sponsors!
Building Momentum through Collaborations

Todd Graham
Executive Director

LEWY BODY DEMENTIA ASSOCIATION

LBDA
LBDA Research Centers of Excellence

• 26 clinical trial ready sites
  • Coordinating Center: Mayo Clinic, Brad Boeve, MD

• Expertise, infrastructure and patient engagement and recruitment resources for LBD clinical trials
Industry Advisory Council (IAC)

Created to provide an interactive and informative council of stakeholder organizations (including researchers, government agencies, pharma/biotech and diagnostics) looking to change the course of LBD diagnosis and treatment.

- Annual in-person meeting
- Two teleconferences a year
- Additional engagement at the trial and project level
LBD Symposium on Biofluid/Tissue Biomarkers

• Sessions:
  • Alzheimer’s disease and novel biofluid biomarkers in LBD
  • Detection of pathogenic alpha-synuclein in peripheral tissues

• January 25, 2021, 12:00 pm to 4:00 pm EST
  • Visit LBDA.org/events to register
Thank You
Introduction to LBD as a Drug Development Priority

James E. Galvin, MD, MPH
Comprehensive Center for Brain Health
Lewy Body Dementia Research Center of Excellence
University of Miami Miller School of Medicine
The Most Common Disease You Never Heard Of

• 2\textsuperscript{nd} most common cause of dementia after AD
  • Causes 10-12\% of irreversible dementia
• Includes Dementia with Lewy Bodies (DLB) and Parkinson’s Disease Dementia (PDD)
  • PDD: Movement Disorder begins 1\textsuperscript{st}, at least 1 year before cognitive problems
  • DLB: Any other pattern
• At least 75\% of PD patients who live 10 years will develop dementia
• More common in men
• May have faster decline than AD
• The combined sum of patients Lewy body dementia is 1.4 million
• Often significant delay to diagnosis and treatment

Other Neurologic Diseases
• Multiple Sclerosis: 1,000,000
• Stroke: 800,000
• Brain Tumors: 700,000
• Muscular dystrophy: 250,000
• Huntington’s disease: 30,000
• Amyotrophic Lateral Sclerosis: 12,000

Lewy Body Dementia Association (LBDA.org)
PDD Epidemiology

- Point prevalence of dementia in PD is close to 30%
- Incidence rate is increased at 4-6 times relative to controls
- At least 75% of PD patients who survive more than 10 years likely to develop dementia
- Mean time from onset of PD to dementia is approximately 10 years
- Old age, more severe motor symptoms (in particular, gait and postural disturbances), mild cognitive impairment at baseline, and visual hallucinations

Lewy Body Dementia Association (LBDA.org); Galvin JE Practical Neurology 2019
DLB Epidemiology

- Prevalence estimates of DLB range from 0% to 5% in the general population and from 0% to 30.5% of all dementia cases
- Incidence rates of 0.1% in the general population, and 3% for all new dementia cases
- A recent review examined 22 studies and reported incidence rates between 0.5 to 1.6 per 1000 person-years, accounting for 3-7% of dementia cases.
- Prevalence estimates ranged from 0.02-63.5 per 1000, higher with increasing age.

Lewy Body Dementia Association (LBDA.org); Galvin JE Practical Neurology 2019
PDD Criteria

- Develops in the context of established PD
  - At least 2 years after a diagnosis of PD
  - Impairment in more than one cognitive domain
    - Attention, executive, visuospatial, memory, language
  - Decline from premorbid level
  - Deficits severe enough to impair daily life
- Exclusion of other dementias
- MMSE below 26 or Impairment in at least two of the following:
  - Months reversed or Seven backward
  - Lexical (category) fluency or Clock drawing
  - MMSE Pentagons
  - 3-Word recall
- Supportive features: apathy, depression, delusions, or daytime sleepiness.
DLB Criteria

Revised criteria for the clinical diagnosis of probable and possible DLB

**Essential** for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

**Core clinical features (the first 3 typically occur early and may persist throughout the course)**

- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations that are typically well-formed and detailed
- REM sleep behaviour disorder, which may precede cognitive decline
- One or more spontaneous cardinal features of parkinsonism: bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity

**Supportive clinical features**

- Severe sensitivity to antipsychotic agents
- Postural instability
- Repeated falls
- Syncope or other transient episodes of unresponsiveness
- Hypersomnia
- Hyposmia

- Severe autonomic dysfunction, eg, constipation, orthostatic hypotension, urinary incontinence
- Hallucinations in other modalities
- Systematized delusions
- Apathy, anxiety, and depression

Research Criteria for Prodromal LBD

• One or more core clinical features may develop years before dementia
  • Spontaneous parkinsonism
  • REM sleep behavior disorder
  • Autonomic complaints (orthostasis, constipation, olfaction)
• Three defined presentations for prodromal phases
  • Mild Cognitive Impairment
  • Delirium-onset Presentation
  • Psychiatric-onset Presentation

McKeith et al, *Neurology* 2020
Symptoms Associated With LBD

**PSYCHIATRIC/BEHAVIORAL**
- Visual Hallucinations
- Other Hallucinations
- Delusions
- Depression, Anxiety, Apathy
- REM Sleep behavior disorder
- Cognitive fluctuations

**CONSTITUTIONAL**
- Loss of Smell
- Constipation
- Urinary Incontinence
- Drooling, Runny Nose
- Dizziness, Lightheaded, Fainting
- Abnormal Sweating
- Sexual Dysfunction

**MOTOR**
- Slowness
- Stiffness
- Imbalance and Falls
- Tremor
- Shuffling Gait
- Myoclonus

**COGNITION**
- Visual Tracking and Attention
- Visual Perception
- Verbal Initiation
- Timed Attention
- Executive Tasks
- Slowed Thinking
- Slowed Processing Speed

**IMAGES**
- A: Slowed Processing Speed
- B: Executive Tasks
- C: Visual Tracking and Attention
- D: Visual Perception
# Cognitive Profiles

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>LBD</th>
<th>bvFTD</th>
<th>VaD</th>
<th>Depression</th>
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<tbody>
<tr>
<td><strong>Episodic Memory</strong></td>
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<tr>
<td>Free recall</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Recognition</td>
<td>+++</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Prompting</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Intrusions</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Semantic memory</td>
<td>++</td>
<td>+</td>
<td>+</td>
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<td>+/-</td>
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<tr>
<td>Procedural memory</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Working memory</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
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<tr>
<td>Insight</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td></td>
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<tr>
<td>Attention</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
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<tr>
<td><strong>Executive functions</strong></td>
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<tr>
<td>Visuospatial skills</td>
<td>++</td>
<td></td>
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<td>+</td>
<td>+</td>
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</tbody>
</table>

+++ Early and severe impairment; ++ moderate impairment; + mild impairment; +/- impairment in some studies but not others; - no significant impairment; x not helpful; ✓ helpful.

Karantzoulis and Galvin, Neurotherapeutics 2014; Galvin JE Practical Neurology 2019
Caregiver Experience With Diagnosis

78% of patients had been diagnosed with something else first
53% AD or other dementia
39% PD or other movement disorder
24% Primary psychiatric disorder

2/3 of patients saw at least 3 physicians before LBD diagnosis

Median time to diagnosis was 12-18 months

62% of diagnosing physicians were neurologists, and only 6% were PCPs

PD = Parkinson’s disease.
Current Treatment Options

**Pharmacology**

(nearly all options are off-label use of medication for DLB)

**Cognitive Symptoms**
- Donepezil (approved for DLB in Japan/Philippines)
- Other cholinesterase inhibitors
- Memantine (?)

**Motor Symptoms**
- Carbidopa
- Levodopa

**Sleep**
- Melatonin
- Clobazam

**Fluctuation Attention**
- Modafinil
- Armodafinil

**Behavior**
- Antidepressants
- Atypical antipsychotics
- Prasugol (?)
- Antiepileptics (?)

**Autonomic**
- Fludrocortisone
- Midodrine
- Droxiclopa
- Trosplum

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## Completed trials in LBD

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Target outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intepridine</td>
<td>DLB</td>
<td>Movement</td>
<td>Negative</td>
</tr>
<tr>
<td>Armodafinil</td>
<td>DLB</td>
<td>Wakefulness</td>
<td>Positive</td>
</tr>
<tr>
<td>Deep brain stimulation</td>
<td>DLB</td>
<td>Memory</td>
<td>No results published</td>
</tr>
<tr>
<td>SYN120</td>
<td>PDD</td>
<td>Cognition and attention</td>
<td>Negative</td>
</tr>
<tr>
<td>Deep brain stimulation</td>
<td>PDD</td>
<td>Safety and cognition</td>
<td>Safe but no cognitive improvement</td>
</tr>
<tr>
<td>Nelotanserin</td>
<td>DLB and PDD</td>
<td>Hallucinations</td>
<td>Safe but not effective</td>
</tr>
<tr>
<td>Nelotanserin</td>
<td>DLB and PDD</td>
<td>REM sleep behavior disorder</td>
<td>Negative</td>
</tr>
<tr>
<td>Pimavanserin</td>
<td>DLB and PDD</td>
<td>Hallucinations and delusions</td>
<td>Positive</td>
</tr>
</tbody>
</table>
## Ongoing Clinical Trials in LBD

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Target symptom or outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mevidalen</td>
<td>DLB and PDD</td>
<td>Cognition and attention</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>PDD</td>
<td>Cognition</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Ambroxol</td>
<td>PDD</td>
<td>Cognition</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Anavex2-73</td>
<td>PDD</td>
<td>Cognition and attention</td>
<td>Ongoing</td>
</tr>
<tr>
<td>GRF6021</td>
<td>PD-MCI and PDD</td>
<td>Safety</td>
<td>Ongoing</td>
</tr>
<tr>
<td>E2027</td>
<td>DLB</td>
<td>Cognition</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>DLB</td>
<td>Safety and tolerability</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
Current Clinical Trials

• Clinical trials in LBD remain a top priority in the NIH ADRD recommendations
• Despite increased numbers of clinical trials for LBD in recent years, randomized controlled trials in LBD lag behind those conducted in other neurodegenerative diseases (e.g., AD, non-demented PD)
• Do not yet address the full range of LBD symptoms
• Primarily focus on symptomatic rather than disease-modifying therapies.
• Recent/ongoing LBD trials remain largely focused on cognitive outcomes but may utilize novel or repurposed agents
• To date, no trials have studied fluctuations, dysautonomia, or agitation, apathy in LBD.
Optimizing Clinical Trial Design

- Clinicaltrial.gov search (12/3/20)
  - 106 registered studies
    - 76 interventional
    - 30 observational
  - 12 interventional studies are active
    - 3 drug
    - 1 measurement
    - 2 procedure
    - 3 imaging agent
    - 3 non-pharmacologic
Summary

• The Lewy body dementias
  • PDD and DLB differ only by timing of movement disorder
  • While clinical criteria lack sensitivity, they are highly specific and correlated strongly with pathology
• For the present time, treatments are largely symptomatic
• There are few active trials of new therapeutics

Unmet needs
• New targets
• Better biomarkers
• Better outcomes
• Capital investment by industry and NIH
Biomarkers at the intersection of AD/DLB Imaging and CSF biomarkers

Douglas Galasko, MD
Professor, Dept of Neurosciences, UCSD
Biomarkers, Endpoints and other Tools (BEST) framework for biomarker qualification
FDA, 2018 - context of use

- Diagnostic
  - Patient Selection
  - Detect a change in the degree or extent of a disease

- Monitoring
  - Indicate toxicity or assess safety
  - Provide evidence of exposure

- Predictive
  - Identify individuals on the basis of effect from a specific intervention or exposure

- Prognostic
  - Stratify patients
  - Enrichment: inclusion/exclusion data

- Pharmacodynamic/Response
  - Efficacy biomarker/surrogate endpoint
  - Show biological response related to an intervention/exposure

- Safety
  - Indicate the presence or extent of toxicity related to an intervention or exposure

- Susceptibility/Risk
  - Indicate the potential for developing a disease or sensitivity to an exposure

Context of Use Examples
Co-pathology
Alzheimer
  - amyloid
  - Tau
Vascular

Neurodegeneration
  synapse loss
  circuit dysfunction
  hypometabolism
  cell death

α-Synuclein pathology

Autophagy
Inflammation
Mitochondrial damage
Lysosomal changes
 Trafficking
CSF total $\alpha$-Synuclein as a biomarker

CSF total $\alpha$-syn is decreased in PD, MSA and DLB, with extensive overlap with normals.

Levels are increased in CJD and slightly in AD.

Blood contamination of CSF results in increased levels.

Mollenhauer, 2011
**α-synuclein seeding assays**

Analogous to seeding assays (RT-QuIC or PMCA) for pathogenic prion proteins

- Sample e.g., CSF, with pathogenic α-synuclein seed
- Recombinant α-synuclein ‘fuel’
- Repeated cycles of agitation and resting

ThT fluorescence is detected as a readout

Analogous to seeding assays (RT-QuIC or PMCA) for pathogenic prion proteins
### α-syn RT-QuIC or PMCA in CSF

<table>
<thead>
<tr>
<th></th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity for PD</td>
<td>88.5</td>
</tr>
<tr>
<td>Sensitivity for DLB</td>
<td>100</td>
</tr>
<tr>
<td>Sensitivity for MSA</td>
<td>80</td>
</tr>
<tr>
<td>Specificity vs disease controls</td>
<td>96.9</td>
</tr>
<tr>
<td>Spec. vs controls and neurodegenerative disease</td>
<td>94</td>
</tr>
<tr>
<td>Pos predictive value</td>
<td>94.7</td>
</tr>
<tr>
<td>Neg predictive value</td>
<td>87.6</td>
</tr>
</tbody>
</table>

Sens and spec for DLB or DLB co-pathology were both > 90%

Shahnawaz, 2017

Bongianni, 2019
40% of DLB in an Amsterdam cohort study had CSF biomarkers indicating AD.

No difference in rate of MMSE decline for AD+ vs AD-.

But shorter interval to nursing home placement or equivalent for AD+. 

Lemstra 2017
Multimodal brain imaging in DLB

Blue: AD
Red: LBD
Green: AD/LBD

Kantarci et al, 2012
Amyloid PET ($^{11}$C-PiB) in DLB

Approximately 50%-80% of patients with DLB have a positive amyloid PET scan

Kantarci et al. *Neurobiology of Aging* 2012
β-Amyloid deposition and rate of disease progression

• Higher PiB retention at baseline associated with accelerated rate of cortical atrophy:
  Medial temporal lobe
  Posterior cingulate gyrus
  Temporal and occipital lobes
  Caudate and putamen

• Higher PiB retention at baseline associated with increase (worsening) in CDR-SOB scores
  • (rho = 0.51; P = 0.02)
Hippocampal Atrophy, APOE ε4 and Survival

- APOE ε4 + and hippocampal atrophy independently predict survival in DLB
- APOE ε4 + with hippocampal atrophy have the lowest survival rates

Conclusions

• Biofluid and imaging markers are complementary in DLB
• Pathological α-Synuclein can be detected by RTQuIC/PMCA in CSF and potentially skin biopsy
• Brain imaging with FDG PET can support a diagnosis of DLB
• Amyloid PET imaging can evaluate concomitant AD pathology
• Concomitant AD is associated with more rapid progression of DLB: clinically and on MRI
• Biomarkers can be deployed to assess brain pathology and improve diagnosis and prognosis in clinical trials for DLB
Thank You for Joining Us Today
To Ask a Question, Use the Chat Function

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Alliance for Aging Research
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