Advances in Diagnosis and Treatment of Lewy Body Dementia

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Parkinson’s Disease
UK Parkinson’s Disease Society Diagnostic Criteria

• Step 1 Diagnosis of Parkinsonism
  – Bradykinesia
  – At least one of following:
    • muscular rigidity
    • 4-6 Hz resting tremor
    • postural instability

• Step 2 Exclusion Criteria for PD
  – Parkinsonism due to other cause
  – Oculogyric crises
  – Sustained remissions
  – Supranuclear gaze palsy
  – Cerebellar signs
  – Early severe autonomic insufficiency
  – **Early dementia**
  – Poor response to L-dopa

• Step 3 Supportive Criteria for PD
  – Three or more of following:
    • Unilateral onset
    • Resting tremor
    • Progressive signs and symptoms
    • Persistent asymmetry
    • Excellent early response to L-dopa with persistence ≥ 5 yrs
    • L-dopa induced dyskinesia
    • Clinical course ≥ 10 years

*J Neurol Neurosurg Psychiatry* (1992) 55:181
Historical Perspective

• “the senses and intellect being unaffected”
  – James Parkinson, 1817

• Described changes in cognition and personality
  – Jean-Marie Charcot 1888

• “Parkinsonism is not necessarily accompanied by any mental change, and the sufferer’s intellectually capacity...may continue unimpaired behind the mask in which his disorder fixes his features”
  – Lord Brain, 1933

Parkinson Disease Dementia

- 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.

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

McKeith et al, Neurology (2005) 65:1863-72
Comparing PDD, DLB and AD

**PDD vs. DLB**
- These groups were nearly identical in all clinical features.
- PDD: Postural instability
- DLB: Spasticity

**PDD vs. AD**
- PDD: male predominance, EPS, cognitive fluctuation, visual and auditory hallucinations, falls, depression and sleep disturbances.

**DLB vs. AD**
- DLB: male predominance, EPS, visual and auditory hallucinations, myoclonus, depression and sleep disturbance

**PDD autopsy:** 38% neocortical LBs only
- 32% neocortical LBs with AD
- 30% subcortical LBs only

Clinical Predictors of LB Pathology

<table>
<thead>
<tr>
<th>Clinical Predictor</th>
<th>Present at any time</th>
<th>Present at 1st visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.50</td>
<td>1.01-2.38</td>
</tr>
<tr>
<td>Any EPS</td>
<td>2.50</td>
<td>1.64-3.82</td>
</tr>
<tr>
<td>Cognitive Fluctuation</td>
<td>4.98</td>
<td>1.63-15.15</td>
</tr>
<tr>
<td>Visual Hallucinations</td>
<td>8.93</td>
<td>2.31-34.50</td>
</tr>
<tr>
<td>Auditory Hallucination</td>
<td>11.76</td>
<td>1.66-83.30</td>
</tr>
<tr>
<td>Neuroleptic Sensitivity</td>
<td>3.75</td>
<td>1.05-13.30</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>3.90</td>
<td>1.27-12.05</td>
</tr>
<tr>
<td>Depression</td>
<td>1.81</td>
<td>1.16-2.82</td>
</tr>
<tr>
<td>Sleep Disturbances</td>
<td>1.98</td>
<td>1.33-2.94</td>
</tr>
</tbody>
</table>

Clinical features such as aphasia, apraxia, agnosia, ApoE not associated

# Lewy Body Composite Risk Score

Please rate the following symptoms as being present or absent for at least 3 times over the past 6 months. Does the patient...

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have rigidity (with or without cogwheeling) on passive range of motion in any of the 4 extremities?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have a loss of postural stability (balance) with or without frequent falls?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have a tremor at rest in any of the 4 extremities or head?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have episodes of illogical thinking or incoherent, random thoughts?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have frequent staring spells or periods of blank looks?</td>
<td></td>
<td></td>
</tr>
<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>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL SCORE**
**Lewy Body Composite Risk Score**

<table>
<thead>
<tr>
<th></th>
<th>Controls (N=25)</th>
<th>AD (N=24)</th>
<th>LBD (N=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72.6 (6.4)</td>
<td>74.8 (6.8)</td>
<td>72.6 (8.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>28.0</td>
<td>58.3</td>
<td>70.0</td>
<td>.01</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.2 (1.9)</td>
<td>13.7 (2.9)</td>
<td>15.4 (2.7)</td>
<td>ns</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>.02 (.11)</td>
<td>3.4 (1.8)</td>
<td>3.9 (2.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.9 (1.2)</td>
<td>25.4 (3.2)</td>
<td>25.3 (3.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Global, z-score</td>
<td>.19 (.65)</td>
<td>-.85 (.78)</td>
<td>-.86 (.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Working, z-score</td>
<td>.13 (.81)</td>
<td>-.57 (.76)</td>
<td>-.56 (.67)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visuospatial, z-score</td>
<td>.25 (.70)</td>
<td>-.56 (1.0)</td>
<td>-1.65 (1.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LBCR Score</td>
<td>0.8 (1.4)</td>
<td>1.0 (1.1)</td>
<td>5.8 (2.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

LBCR Score correlates to Cognitive Profiles:
- Global (r= -.563, p=.003)
- Visuospatial (r=-.529, p=.005)
- Working (r=-.369, p=.058)

**AUC: 0.965 (95%CI: 0.91-1.0)**
- Using Cut-Off: 3
  - Sensitivity: 91%
  - Specificity: 89%

*Karantzoulis S, Galvin JE, Clin Trans Gerontol 2013*
# Lewy Body Composite Risk Score

<table>
<thead>
<tr>
<th></th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD</td>
</tr>
<tr>
<td>Age</td>
<td>80.9 (6.5)</td>
</tr>
<tr>
<td>Gender, %M</td>
<td>33.9</td>
</tr>
<tr>
<td>Education</td>
<td>15.9 (3.6)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>2.2 (1.1)</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>5.9 (3.5)</td>
</tr>
<tr>
<td>FAQ</td>
<td>9.9 (8.3)</td>
</tr>
<tr>
<td>Mini-PPT</td>
<td>9.9 (2.3)</td>
</tr>
<tr>
<td>MMSE</td>
<td>19.9 (5.8)</td>
</tr>
<tr>
<td>NPI</td>
<td>7.9 (5.9)</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>6.8 (4.5)</td>
</tr>
<tr>
<td>Daytime Alertness</td>
<td>7.1 (2.0)</td>
</tr>
<tr>
<td><strong>Lewy Body Composite</strong></td>
<td><strong>2.8 (1.4)</strong></td>
</tr>
<tr>
<td>Parkinsonism, %</td>
<td>38.9</td>
</tr>
<tr>
<td>Bradykinesia, %</td>
<td>50.0</td>
</tr>
<tr>
<td>Rigidity, %</td>
<td>11.1</td>
</tr>
<tr>
<td>Tremor, %</td>
<td>5.6</td>
</tr>
<tr>
<td>Postural Instability, %</td>
<td>27.8</td>
</tr>
<tr>
<td>Falls, %</td>
<td>45.5</td>
</tr>
<tr>
<td>Hallucinations, %</td>
<td>11.1</td>
</tr>
<tr>
<td>Fluctuations, %</td>
<td>41.1</td>
</tr>
<tr>
<td>RBD, %</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Galvin JE, In Preparation 2014
Current Project

Healthy Aging

PD (no dementia)

MCI

PD-MCI

AD

PDD
Retrospectively Characterizing PD-MCI

Johnson and Galvin, *Under Review 2014*
Retrospectively Characterizing PD-MCI

<table>
<thead>
<tr>
<th>Non-Significant Subtests</th>
<th>Intercept (α)</th>
<th>Slope in Pre(β₁)</th>
<th>Slope in Post (β₂)</th>
<th>Predicted Change(δ) Relative to Diagnosis</th>
<th>CDR Sum of Boxes at Time of Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logical Memory</td>
<td>-0.05 (0.15)</td>
<td>0.08 (0.05)</td>
<td>-0.04 (0.02)</td>
<td>-6.65 (1.91)</td>
<td></td>
</tr>
<tr>
<td>Associate Learning</td>
<td>0.07 (0.16)</td>
<td>0.03 (0.02)</td>
<td>-0.06 (0.02)</td>
<td>-4.99 (1.97)</td>
<td></td>
</tr>
<tr>
<td>Boston Naming</td>
<td>0.35 (0.23)</td>
<td>-0.03 (0.05)</td>
<td>-0.07 (0.02)</td>
<td>-5.71 (2.85)</td>
<td></td>
</tr>
<tr>
<td>Trailmaking A</td>
<td>50.52 (8.22)</td>
<td>1.07 (1.58)</td>
<td>2.28 (0.70)</td>
<td>-5.82 (2.85)</td>
<td></td>
</tr>
<tr>
<td>Digits Forward</td>
<td>0.43 (0.15)</td>
<td>0.00 (0.04)</td>
<td>-0.06 (0.02)</td>
<td>-4.87 (2.67)</td>
<td></td>
</tr>
<tr>
<td>Word Fluency</td>
<td>0.04 (0.39)</td>
<td>-0.12 (0.04)</td>
<td>-0.08 (0.03)</td>
<td>-3.86 (3.25)</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates a significant difference between Phase 1 and Phase 2

Johnson and Galvin, *Under Review* 2014
Prospectively Characterizing PD-MCI

- To better characterize the cognitive profile of PD, we examined:
  - Individual domain scores on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a measure of global neurocognitive functioning
  - Neuropsychological Assessment Battery (NAB)-Executive Functions module (NAB-EF), a battery of judgment, conceptualization, mental flexibility, verbal fluency

ROC Analyses

**HC vs. PD-I**
- RBANS: 0.994 (.97-1.0)
- NAB-EF: 0.925 (.82-1.0)

**PD vs. PD-I**
- RBANS: 0.890 (.74-1.0)
- NAB-EF: 0.844 (.69-1.0)

Karantzoulis and Galvin, *In Preparation 2014*
High Density EEG

Sensor array of an HCGSN 256-electrode cap with the first 30 channels in red.
Changes in Spectral Content

Larson-Prior and Galvin, In preparation 2014
Resting State Network Analyses

Patterns of Temporal Coherence Within and Across Systems

Based on 39 ROIs

Based on 225 ROIs

Modifications include:

• The addition of ‘motion scrubbing’ to remove head motion artifacts
• A larger number of ROIs – from 39 to 225 which vastly expands representation of visual areas and provides fuller coverage of the cortex and subcortical structures
Frontal-Parietal Executive Network

A. CONTROL

B. PARKINSON’S DISEASE

Larson-Prior and Galvin, In preparation 2014
**Cingulo-Opercular Network**

**A:** Resting state functional connectivity matrices show the inter-network connectivity of the cingulo-opercular network. Reductions in inter-network connectivity in both MCI groups relative to Control and PD.

**B:** Statistical analysis of connectivity changes between Control and PD using the Network-based statistic method. The highlighted edges differed (1000 permutations, false discovery rate, p<0.05) significantly in connections between somatomotor and cingulo-opercular networks.

Larson-Prior and Galvin, *In preparation 2014*
Visual Network

Larson-Prior and Galvin, In preparation 2014
Dopamine Metabolism

DOPAL: 3,4-dihydroxyphenylacetaldehyde
ALDH: Aldehyde dehydrogenase

Intranigral injection of DOPAL causes nigral cell death and AS aggregation.

Burke Panneton, Kumar, and Galvin, Acta Neuropathologica 2008; Panneton, Kumar, Burke and Galvin, PLoS One 2010
Diffusion Kurtosis Imaging

Figure 2: Comparison of DTI and DKI fiber tracking showing the intersection between corpus callosum and superior longitudinal fasciculus and the intersection between corpus callosum and corona radiata. DKI-based fiber tracking, in contrast to DTI-based, is able to resolve intravoxel fiber crossing.
Diffusion Imaging of Nigral Tracts

Fieremans and Galvin, In preparation 2014
White matter changes: Control vs PD

Mean kurtosis MK

Axial kurtosis $K_{||}$

1. From NC to PD, changes are in kurtosis in major White Matter tracts
2. From PD into PDI the additional change is in smaller White Matter tracts
3. Significant ROI differences: cingulum, hippocampus, fornix, and corpus callosum
4. These changes correlate with changes in Visuospatial, Executive, and Memory domains

Fieremans and Galvin, *In preparation 2014*
# Treatment Options

<table>
<thead>
<tr>
<th>Pharmacology*</th>
<th>Non-Pharmacology</th>
</tr>
</thead>
</table>
| • Cognitive Symptoms  
  – Cholinesterase Inhibitors  
  – Memantine (?)  
| • Remove trigger, distract/redirect  
| • Motor Symptoms  
  – Carbidopa/Levodopa  
| • Caregiver education and support  
| • Fluctuation and Attention  
  – Modafinil, Armodafinil  
| • Adult day programs  
| • Behavior  
  – Antidepressants  
  – Atypical Antipsychotics  
  – Prazosin (?)  
  – Antiepileptics (?)  
| • Psychotherapy techniques  
  – Memory retraining  
| • Sleep  
  – Melatonin  
  – Clonazepam  
| • Stimulation-oriented treatment  
  – Music  
  – Art  
  – Recreational or social therapies  
  – Exercise  
  – Dance  
| • Autonomic  
  – Fludrocortisone  
  – Midodrine  
| • Montessori-based activities  
  – Memory BINGO  
  – Group sorting  

* Nearly all options are off-label use of medication
What we learned....

• The clinical picture of LBD includes male gender, visual and auditory hallucinations, sensitivity to neuroleptics, depression, fluctuations, myoclonus and sleep disturbances.

• Use of the Lewy Body Composite Risk Score can significantly improve ability to diagnose and classify dementia syndromes thought to be attributable to Lewy Body pathology

• The cognitive picture of LBD includes declining working memory preceding a decline in the ability to use visual imagery in problem solving. These cognitive problems culminate in deficits in retrieval from long term memory.
  – Episodic memory tasks changed at time of dementia diagnosis.
  – Visuospatial abilities were the strongest indicators
  – Language was the weakest indicators
What we learned...

• The bioanatomical basis appears to loss of integrity in neural networks
  – Reorganization of Visual, Executive Control, and Error Checking networks
  – Spectral changes and diminished coherence on hdEEG
  – Disruption of white matter connectivity

• Classic tests of episodic memory may not be sufficient to detect and quantify cognitive decline in LBD.

• A decline in accessing crystalized information is a harbinger of diagnosis, probably representing an accumulation of subcortical pathology affecting memory retrieval and mental flexibility prior to a significant accumulation of cortical pathology affecting new learning.

• We can explore correlates between functional connectivity (measured by resting BOLD fMRI), brain synchrony (measured by hdEEG) and white matter integrity (measured by DKI) to develop biomarkers of disease progression and response to clinical interventions.

• Possible end-points for clinical trial design which are needed to promote new drug discovery and testing.
Questions?
Patient and Caregiver Experience in Lewy Body Dementia

Lewy Body Dementia Symposium at NYU Langone Medical Center
Yael Zweig, ANP-BC, GNP-BC

October 21, 2014
## Summary of Dementias

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Frequency</th>
<th>Typical Age</th>
<th>Family History</th>
<th>Early Clinical Features</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease (AD)</td>
<td>60-65%</td>
<td>70-80’s</td>
<td>Yes</td>
<td>Memory disorder</td>
<td>Senile plaques Neurofibrillary tangles</td>
</tr>
<tr>
<td>Lewy Body Dementia (LBD)</td>
<td>10-15%</td>
<td>60-70’s</td>
<td>No</td>
<td>Parkinson-like features (slowness, tremor) Visual hallucinations Fluctuations (staring spells) Sleep disturbances</td>
<td>Lewy bodies Senile plaques (80%) Neurofibrillary tangles (rare)</td>
</tr>
<tr>
<td>Vascular Dementia (VaD)</td>
<td>10-15%</td>
<td>70-80’s</td>
<td>No</td>
<td>Executive disorder Depression Neurological deficits (depending on location of stroke)</td>
<td>Strokes</td>
</tr>
<tr>
<td>Frontotemporal Degeneration (FTD)</td>
<td>5-10%</td>
<td>50-70’s</td>
<td>Yes</td>
<td>Behavior and Personality changes Language disturbance</td>
<td>Neurofibrillary tangles Intraneuronal inclusions</td>
</tr>
<tr>
<td>Depression</td>
<td>n/a</td>
<td>n/a</td>
<td>Yes</td>
<td>Mood changes Memory disturbances that often change with mood</td>
<td>May have Senile plaques</td>
</tr>
</tbody>
</table>
Lewy Body Dementia
Clinical Features

• Central feature is a progressive dementia
  • Difficulty with attention and executive tasks may be present before significant memory impairment is seen
• Core features (need at least 2 present for a diagnosis)
  • Fluctuating cognition- variation in attention and alertness
  • Recurrent visual hallucinations (60-70%)
  • Parkinsonism
• Suggestive features
  • REM sleep behavior disorder
  • Sensitivity to neuroleptic medications
  • Low dopamine transporter uptake in basal ganglia on SPECT or PET imaging
Lewy Body Dementia
Clinical Features

• Supportive features
  • Recurrent falls and syncope
  • Transient, unexplained loss of consciousness
  • Severe autonomic dysfunction
  • Other hallucinations
  • Systematized delusions
  • Depression
DLB Diagnosis

- Probable DLB: Two core features or one core feature and one suggestive feature
- Possible DLB: One core feature, or one or more suggestive features

![Imagery](A,B,C,D)
Lewy Body Dementia

Similar distribution and severity of Lewy body pathology

Dementia with Lewy Bodies
- Resting tremor less common
- More likely to be rigid

Parkinson’s disease dementia
- Presence of motor symptoms ≥ one year before cognitive decline
Challenges in LBD diagnosis

• Symptoms overlap with AD, PD, and psychiatric diseases leading to misdiagnosis and under recognition

• AD can have mild parkinsonism and psychiatric features

• Clinical diagnosis requiring knowledge and skill

• Comprehensive history necessary for diagnosis

• Lack of familiarity of LBD among healthcare providers

• Wrong initial diagnosis given 78% of time in one sample
How is LBD different from AD?

- Early changes in visuospatial ability, attention, executive function (judgment, organization, planning)
- Memory impairment much more likely to be reported in AD
- Apathy, loss of interest in hobbies, depression
- Gait problems, tremor, stiffness
- Purposeless hyperactivity, psychiatric symptoms
- Visual hallucinations more commonly present in early years of disease
- More insight into cognitive deficits
- Episodic memory deficit improves with cuing
Why is LBD unique?

• All patients don’t look the same

• Stress from lack of knowledge and added burden of constantly ensuring patient safety

• Poor tolerability to medications that may be used to treat common symptoms

• Treatment depends on symptoms and not all symptoms may require a medication

• Balance in treating symptoms without exacerbating other features
Why is LBD unique?

- Dementia
- Parkinsonism
- Behavior
- Autonomic symptoms
Caregiver Experience

• Challenges in obtaining a diagnosis

• Patients see multiple physicians over multiple visits before receiving a diagnosis

• 51% diagnosed in the first year, 31% more than 2 years for diagnosis

• Initial diagnosis was initially given as a disorder other than LBD in 78% of cases

• 50% see 2 or more clinicians for LBD related concerns
Caregiver Experience

- 77% of caregivers report difficulty finding a physician with knowledge of treating LBD

- Inadequate discussion of prognosis, course of disease, provision of patient and caregiver education, or referral to community services

- Higher caregiver burden than in other dementias
  - Greater functional disability and earlier loss of independence
  - More prominent behavioral and emotional changes
  - Lack of empathy from support system and difficulty locating other people with similar concerns
Caregiver Burden

- Medium to high levels of burden reported by caregivers of LBD patients with moderate to severe levels of disability

- No difference in burden scores by initial presentation (motor or cognitive)

- Higher burden in spouses, particularly when patients have disturbances in mood and sleep

- Increase in burden with apathy, anxiety, and psychotic features

- Falls are not a risk for burden
Caregiver Burden

• One quarter of LBD caregivers feel no one understands what they are going through

• 40% report feeling isolated due to lack of knowledge about LBD—less information available about LBD and less public recognition

• Most respondents were not receiving paid help and 38% received no help

• 64% had a crisis situation in the past year

• LBD caregivers are more likely to report worry about performance (especially male caregivers)
Caregiver Support

• Help is not “one size fits all”
  • Support groups
  • Individual or family counseling
  • Meal or coffee with a friend
  • Journal
• When others offer help- take it
• If others don’t offer help- ask for what you need
  • “Just do it”
• Enjoyable activities together
• Self care before caregiving
Caregiver “Tools of the Trade”

- Understand symptoms
- Be an advocate
- Think ahead and be proactive
- Assess patterns
- Investigate collaborative models of care
Patient Experience

• Neuropsychiatric symptoms and dependence in instrumental activities of daily living are better determinants of QoL than cognitive function

• Patients may underreport symptoms because they are nonspecific or assume they are not associated with the disease

• Autonomic dysfunction often the most bothersome
  • Especially sialorrhea, urinary and bowel symptoms, postural dizziness, and fatigue
  • Associated with poorer overall perception of general health
How to improve patient experience?

**Cognition**

• Treat cognitive symptoms

  • Cholinesterase inhibitors may provide a benefit in cognition, hallucinations, delusions, apathy, and anxiety, activities of daily living, and may improve mortality

  • Namenda may provide cognitive benefits in memory and attention

  • Avoid medications that may worsen cognition
How to improve patient experience?

Behavior and Mood

• Anticipate triggers for behavioral symptoms
• Anxiety and depression can be diagnosed many years before DLB diagnosis and can be treated
• Antipsychotic medications can cause neuroleptic malignant syndrome, change in movement, worsening cognition, or sedation
• Delusions
• Hallucinations
  • Correct vision, bright lights in the evening and no lights at night
  • Take away contributing medications
How to improve patient experience?

**Movement**

• Avoid medications that worsen symptoms (antipsychotics, nausea, certain anticholinergics for tremor)
• Treatment of choice is Sinemet (Carbidopa-Levodopa) when motor symptoms > neuropsychiatric features
• PT, OT, speech and/or swallow therapy
• Fall precautions
• Avoid slip rugs
• Modification of living spaces
• Assistive devices
How to improve patient experience?

**Autonomic Dysfunction**

- **Constipation**
  - May be present a decade before diagnosis
  - Under recognized and poorly treated - 80-89% of PD patients have constipation and/or diarrhea
  - High fiber, fluids, regular exercise, stool softeners

- **Postural hypotension**
  - May become more noticeable later in disease
  - Weakness, fatigue, dizziness, syncope
  - Increase salt (>8g) and water (2-2.5L/day)
  - Compression stockings
How to improve patient experience?

**Autonomic Dysfunction**

- Sialorrhea
  - Anticholinergics or botulinum toxin in salivary glands

- Urinary symptoms
  - Urgency, frequency, nocturia
  - Choose medications that are less likely to cross the blood-brain barrier
  - Investigate other age related conditions
How to improve patient experience?

**Sleep**

- Excessive daytime sleepiness
  - Degenerative changes of the arousal system
  - Evaluate for contributing factors (sleep apnea)
- Sleep hygiene
- Stimulant medications

- REM sleep behavior disorder
  - Remove sharp objects, creating barriers with pillows and mattress, moving mattress to the floor
  - Sleep partners can be incorporated into dreams as attackers increasing risk
- Melatonin, Clonazepam as second line
Patient “Tools of the Trade”

- Treat symptoms that are most bothersome, *when* they are most bothersome
- Non medication interventions are just as important as medication
- Mental and physical activity
- Pursue hobbies, interests, intellectual engagement and social endeavors
- Be creative
Where to get help

• Utilize Parkinson’s disease and Alzheimer’s disease resources

• LBDA, Alzheimer’s Association, Alzheimer’s Foundation, APDA

• Outpatient or home therapy

• Home nursing services (VNS Behavioral Health program)

• Respite care

• Day programs
Resources

• Lewy Body Dementia Association www.lbda.org
• American Parkinson Disease Association http://www.apdaprkinson.org/
• National Parkinson Foundation http://www.parkinson.org/
• NYU Center for Cognitive Neurology http://memory.med.nyu.edu/
• Alzheimer's Association http://www.alz.org/nyc/
• US Health and Human Services www.alzheimers.gov
• ADEAR http://www.nia.nih.gov/alzheimers
• Alzheimer’s Foundation www.alzfdn.org
• Family Caregiver Alliance http://www.caregiver.org
• Alzheimer’s store http://www.alzstore.com/
• National Academy of Elder Law Attorneys www.naela.org
• Geriatric care management http://memberfinder.caremanager.org/
Thank You

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MIND, MOOD & MEMORY
IN PARKINSON’S DISEASE

“My therapy is quite simple: I wag my tail and lick your face until you feel good about yourself again.”

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Jori Fleisher, MD
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10/21/2014
Quick review of Parkinson’s Disease (PD):
  - Who, When & What
  - Depression & anxiety
  - Apathy
  - Cognitive changes
  - Impulse control disorders
  - Support
First described in 1817, based on SIX patients!
- Many of the cardinal features
- “Sense and intellect being unaffected”

100-330 cases per 100,000

1 million each in the US & Europe

1-2% of people >60 years old; 3-4% of people >80
- 2nd most common neurodegenerative disease
MOTOR & NONMOTOR MANIFESTATIONS

Motor:
- Tremor
- Rigidity
- Bradykinesia
- Postural instability

Nonmotor:
- Loss of smell
- Sleep disturbances
- Constipation
- Autonomic dysfunction
- Fatigue
- Cognitive changes and dementia
- Hallucinations and psychosis
- Depression & Anxiety
- Apathy
- Impulse control disorders
- Pain & sensory changes
- Skin changes
MOOD & MEMORY SYMPTOMS ASSOCIATED WITH PD
30-40% of people with PD will have significant depressive symptoms at some time

- NOT a reaction to the diagnosis
- PART of the underlying pathologic changes in the brain

Symptoms of depression:
- Sadness, feeling “blue” or “down”
- Loss of interest in activities that usually give you pleasure
- Feelings of guilt, hopelessness, or worthlessness
- Low energy
- Trouble concentrating
- Decreased appetite
- Psychomotor slowing
- Trouble sleeping
- Suicidal thoughts
Non-medication treatments:
- Social involvement, support groups, exercise
- Cognitive-behavioral therapy

Medication
- Selective serotonin reuptake inhibitors (SSRIs)
  - Fluoxetine, sertraline, paroxetine, citalopram, escitalopram
    - Prozac, Zoloft, Paxil, Celexa, Lexapro
  - Side effects: Sexual dysfunction, drowsiness, weight gain, insomnia, anxiety, headache, tremor, serotonin syndrome
- Tricyclic antidepressants (TCAs)
  - Second-line; higher risk of side effects but proven effective in PD
  - Nortriptyline, amitriptyline, imipramine
    - Pamelor, Elavil, Tofranil
  - Side effects: Confusion, change in mental status, drowsiness, urinary retention, blurry vision, dry mouth, weight gain
- Other antidepressants
Up to 40% of people with PD have significant anxiety

Symptoms
- Loss of confidence, fear of social occasions & public speaking
- Generalized anxiety state
- On/off anxiety states

Treatment options
- Medication-related on & off anxiety: PD medication adjustments
- Psychotherapy
- Anti-anxiety medications: clonazepam, lorazepam, buspirone
- Anti-depressant medications
Apathy: *loss of motivation or initiative to do usual activities*
- Some overlap with depression, but should be distinguished by preserved pleasure in activities once involved

17-70% of people with PD

Signs & symptoms
- Overlap w PD symptoms
  - masked face may lead observers to think person is uninterested
  - slowness of movement may be interpreted as disinterest
- When severe, loss of initiative → restriction of activities, speech
- May be more noticeable/bothersome to spouse, caregivers
- Influenced by cognitive impairment and depression
APATHY

Treatment options

- Treat underlying cognitive problems & depression
- Individualized daily schedule, vary activities
- Education, education, education!
- Caregiver support, respite
IMPULSE CONTROL DISORDERS

- Definition: Problem or pathological gambling, compulsive buying, compulsive sexual behavior, and/or binge or compulsive eating

- How common?
  - 5% gambling
  - 3.5% compulsive sexual behavior
  - 6% compulsive buying/shopping
  - 4% compulsive eating
  - 4% 2 or more of the above

- Who?
  - More common in younger people, unmarried, smokers, family history of gambling addiction
  - Dopamine agonists (ropinirole, pramipexole, rotigotine) increase risk

- Treatment: STOP THE OFFENDING MEDS... other interventions being studied
~30% of people with PD have some degree of cognitive change in specific areas

Things that can be affected:
- “Tip-of-the-tongue” phenomenon
- Attention, multitasking
- Active memory
- Executive function
- Visuospatial function
- Speed of thinking

Things that do not change:
- Verbal functions
- Reasoning
Younger, shorter duration of PD symptoms, & tremor-predominance = **lower risk** of developing cognitive decline

**Treatment approach:**
- Exclude other known causes of altered mental status, depression
- Evaluate medication list and wean those that can worsen cognition
- Simplify drug regimen to balance motor and cognitive difficulties
- Structured, familiar environment; individualized daily schedule
- Cognitive rehabilitation therapy
- Medications as needed: donepezil, rivastigmine, memantine
Definition:

- Progressive decline in thinking or behavior from a prior level of functioning in 1 or more of:
  - Memory, reasoning, language, visual processes, executive functions, behavior, social-interpersonal behaviors, personality
- Interferes with customary activities of daily life and social relationships
- Caused by permanent damage to or death of the brain’s nerve cells
DEMENTIA

Causes:

- #1 is Alzheimer’s Disease; 10% of people >65y, 40% of >85y
- 20-70% with PD will develop dementia at some point
  - As person with PD ages, at risk of PD dementia, BUT ALSO, may have Alzheimer’s or other causes of dementia (unrelated to PD)
- Other causes of dementia: multiple strokes, frontotemporal dementia, chronic alcoholism, B12 deficiency, syphilis, delayed effects of chemotherapy and/or radiation, AIDS, etc.
HALLUCINATIONS

“A false or distorted sensory experience that appears real; generated by the mind rather than by external stimuli, and may be seen, heard, felt, or even smelled or tasted”

6-60% of people with PD develop hallucinations at some point, typically later in the disease, often caused by or made worse by PD medications

Types of hallucinations

- Illusion: mistaking a real object for something else
- Sensory illusions
  - Feeling of someone walking past/behind you, sensing a “presence”
- Visual hallucinations
  - “Simple”: flashes of light, geometric shapes moving around
  - “Complex”: well-formed animals, objects, and humans.
  - Recognized as being false
DON’T LET THINGS GET THIS FAR!
We can offer medications, but we can also offer...

- Physical, occupational, dance, and speech therapies specifically designed for & sensitive to the needs of people with PD
- Counseling
  - Referrals to psychologists, psychiatrists, counselors, social workers
  - Referrals to home care services, respite care services
- Support groups
- Websites
  - *Just because it’s online, doesn’t mean it’s true!*
  - Reliable websites with active patient & caregiver participation
Just because it’s online, doesn’t mean it’s true!

- National Parkinson Foundation: www.parkinson.org
- Parkinson’s Disease Foundation: www.pdf.org
- Michael J. Fox Foundation for Parkinson’s Research: www.michaeljfox.org
- American Parkinson Disease Association: www.apdaparkinson.org
- Parkinson Research Foundation: www.parkinsonresearchfoundation.org
- Worldwide Education and Awareness for Movement Disorders: www.wemove.org
Depression, anxiety, and apathy may happen early in PD and should not be ignored
- Part of the underlying disease, not just a reaction
- As bothersome as motor problems
- Treatable

Impulse control disorders can happen from anti-PD medicines or from PD itself
- Be aware and be ready to report it!

Cognitive changes may happen later & should not be ignored
- Important to rule out other causes
- Important to adjust medications

Don’t forget the CAUTIONS:
- Just because these can happen, does not mean they will!
- If they are happening, your doctor needs to know! We can help!
QUESTIONS?
REM Sleep Behavior Disorder and Cognitive Fluctuations in Dementia with Lewy bodies

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What goes on when you sleep:

1. Your brain recharges
2. Your body releases important hormones
3. Your cells repair themselves
DREAM SLEEP: Rapid Eye Movement (REM) sleep

REM Sleep Behavior Disorder (RBD)
REM Sleep Behavior Disorder (RBD)

- Loss of REM sleep paralysis
- Movements match the dream
- More common in men
- Actions can result in injuries

It is a neurologic condition
RBD: Sorting out Myth from the Facts

- Not Post Traumatic Stress Disorder (PTSD)
- Not a seizure disorder

Not sleepwalking

Not sleep apnea

Not restless legs syndrome
RBD: Why is it important?

• Helps us to correctly diagnose DLB
• RBD is a risk factor for DLB
RBD: What should we do?

- Stay safe (pillows, lower bed, move sharp objects).
- Separate rooms may mean a better night’s sleep.
- Pharmacologic treatment options: low dose clonazepam, melatonin.

Should I wake him/her when I notice movements?

- only if safety is an issue.
- RBD does not typically disrupt sleep, but repeated waking may lead to greater daytime sleepiness and REM rebound.
Daytime Sleepiness in DLB
Confirmed by caregiver report and sleep studies
• occurs early in the condition
• differs from normal aging and Alzheimer’s disease
• not due to poor sleep the night before.

So….Why the sleepiness?

Lewy bodies may interfere with the “wake” cells in the brain
Like a switch, we are “awake” or “asleep”.

If there are fewer active “wake” cells, it may be easier for the “sleep” cells to switch on.
Sleep

Wake
Can someone be in a state of consciousness that is neither awake or asleep?
We all have daily **biological** fluctuations.

Growth Hormone  
Melatonin  
Testosterone  

Cortisol

---

![Graph showing daily fluctuations of body temperature](image-url)
We all have daily **cognitive** fluctuations

Variability: stress, pain, sleep, sickness, medication, alcohol....
DLB Fluctuations

Task performance

Alert
Lucid
Can carry out certain tasks

Time

good
poor

Drowsy
Sleepy
Zoned out
Not making sense
Unable to do certain tasks
Neurotransmitter important for Attention: Low levels in early DLB

Time

good

poor

Task performance

Drowsy

Sleepy

Trouble communicating

Unable to do certain tasks
Cholinesterase inhibitors boost the availability of this neurotransmitter.

Alert  Lucid  Can carry out certain tasks

Time  

Task performance

good  poor
What can we do about DLB Fluctuations?

• Look into physical contributors
  • infection, pain, medications, alcohol, apnea etc
• Consider treatment options
• Use routines
• Incorporate exercise
• Recognize a fluctuation when you see it
  • “predict the unpredictable”
RBD, Daytime sleepiness, and DLB Fluctuations

• Any one or combination may occur in DLB

• If you suspect one of these issues, get it evaluated
  • We may be able to manage it better, or avoid making it worse

• Try to get a good night’s sleep
  • For immune function, tissue repair, maintaining biologic rhythms
  • For better cognitive function
  • For stress management
Collaborators: Mayo Clinic

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