Expert Briefings
Parkinson's Foundation

Let's Talk About Dementia

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Expert Briefings
Parkinson's Foundation

Let's Talk About Dementia

James Beck, PhD
Chief Scientific Officer, Parkinson's Foundation

James Leverenz, MD
Director, Cleveland Clinic Lou Ruvo Center for Brain Health

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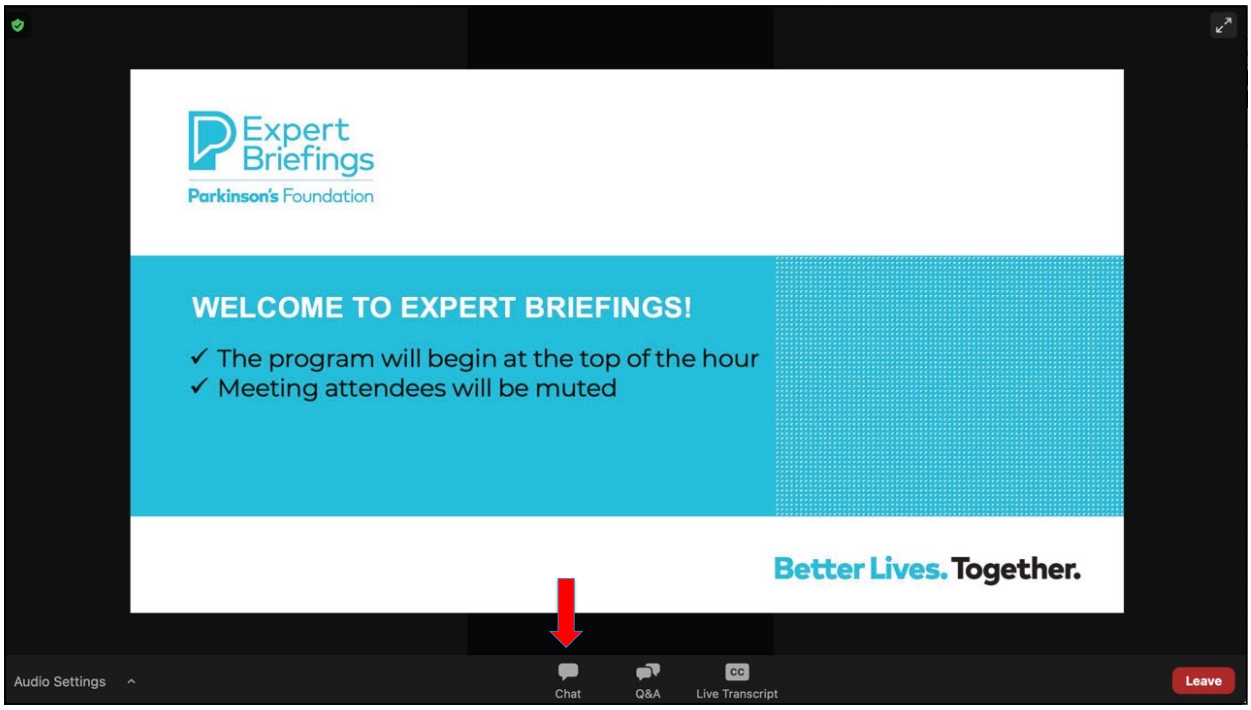
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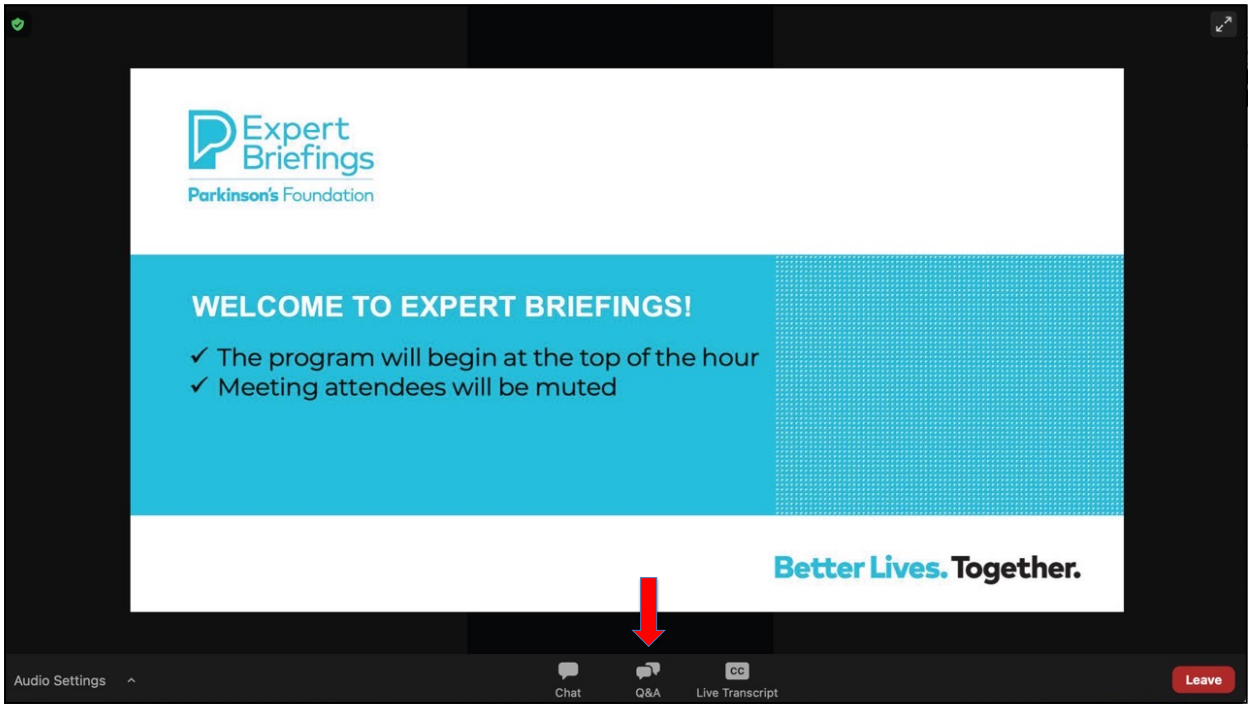
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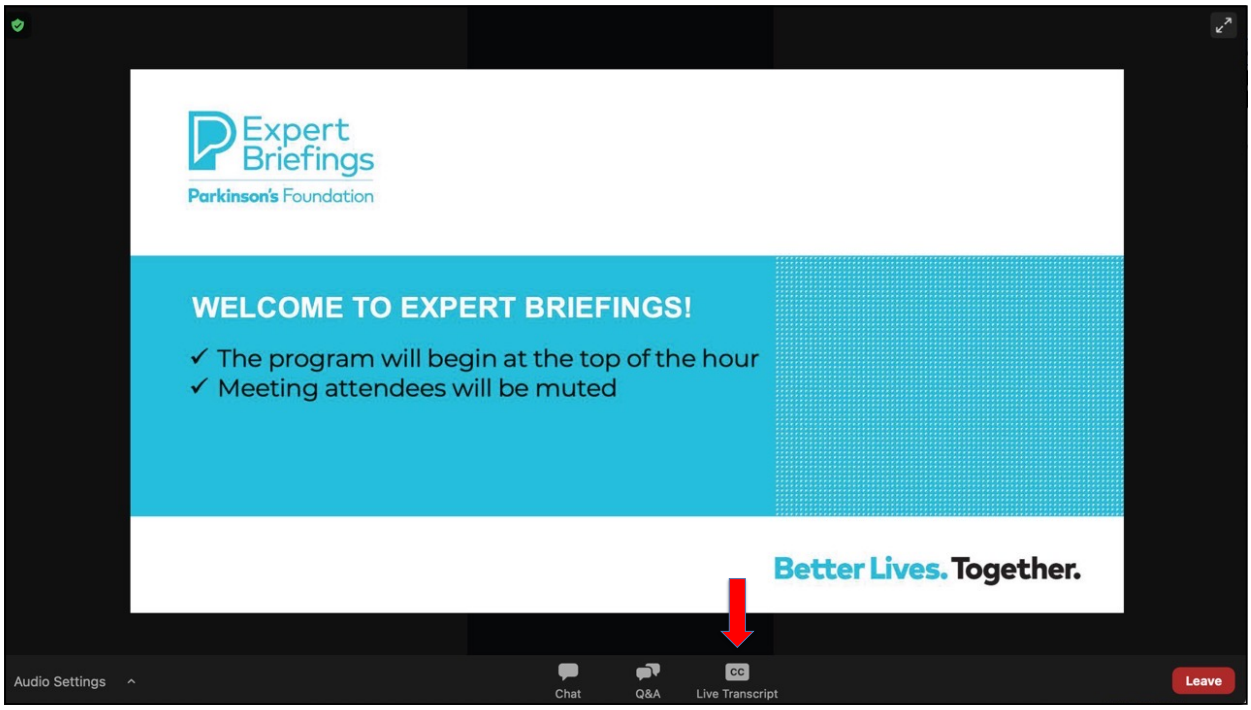


Our Mission

Parkinson's Foundation

The Parkinson's Foundation makes life better for people with Parkinson's disease by improving care and advancing research toward a cure. In everything we do, we build on the energy, experience and passion of our global Parkinson's community.

We have everything you need to live better with Parkinson's.

Our Goals

To help our global community live better with Parkinson's, we pursue **three goals:**

- **Improve care for everyone with Parkinson's**
- **Advance research toward a cure**
- **Empower and educate our global community**

For Your Convenience

RECORDING

Expert Briefings are recorded and archived on **Parkinson.org/ExpertBriefings** within one week

SLIDES

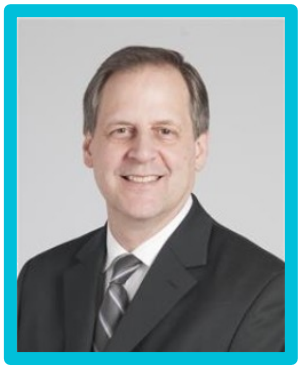
Download today's presentation via link in the chat.

Poll: Getting to Know You

What best describes your connection to Parkinson's disease?

- Person with PD
- Spouse/Partner
- Parent has/had PD
- Other family
- Healthcare Professional
- Physician/Clinician
- Scientist/Researcher
- Nurse/Nurse Practitioner
- Other

Meet Your Presenter



James Leverenz, MD

Director, Cleveland Clinic Lou Ruvo Center for Brain Health

Expert Briefing: Let's Talk About Dementia

James B. Leverenz, MD

Cleveland Lou Ruvo Center for Brain Health

Neurological Institute

Cleveland Clinic

Supported by Alz Assn, Department of Defense, GE Healthcare , LBDA, National Institute of Health, Jane and Lee Seidman Fund

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Disclosures

- Consulting:
  - Citibank, Vaxxinity

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Overview

- Definitions
- The Lewy Body Associated Dementias
  - Mild Cognitive Impairment (MCI)
  - Dementia
- Treatment
- Research

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Dementia

NIA/AA:

"Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that: "

- Interferes with ***ability to function*** at work or at usual activities
- …a ***decline from previous levels*** of functioning…
- …Cognition/behavior involve at least two cognitive domains:
  - Memory, executive function, visuospatial, language, behavior

McKhann et al., *Alzheimer's & Dementia, 1-7, 2011.*

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Mild Cognitive Impairment (MCI)

NIA/AA:

"Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that: "

- ~~Interferes with ***ability to function*** at work or at usual activities~~
- …a ***decline from previous levels*** of functioning…
- …Cognition/behavior involve at least two cognitive domains:
  - Memory, executive function, visuospatial, language, behavior

McKhann et al., *Alzheimer's & Dementia, 1-7, 2011.*

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Parkinson's Disease

- **Tremor (resting)**
- **Rigidity**
- **Bradykinesia**
- **Postural instability**

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Pathology in Parkinson's Disease

- Clinical history of parkinsonism
- Neuronal loss and ***Lewy body inclusions*** in the substantia nigra, locus coeruleus, basal forebrain and cerebral cortex

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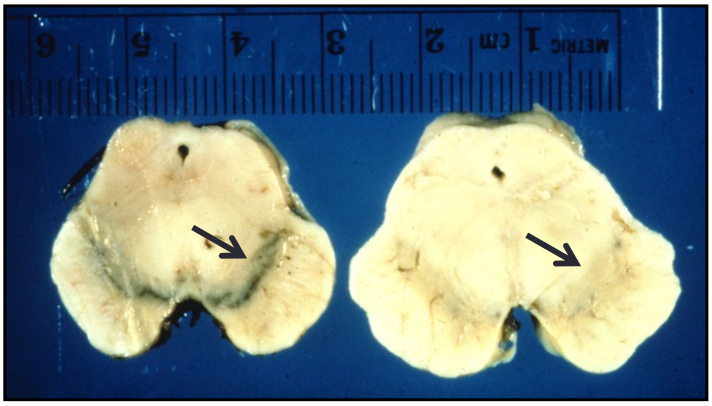
Pathology in Parkinson's Disease



Substantia Nigra

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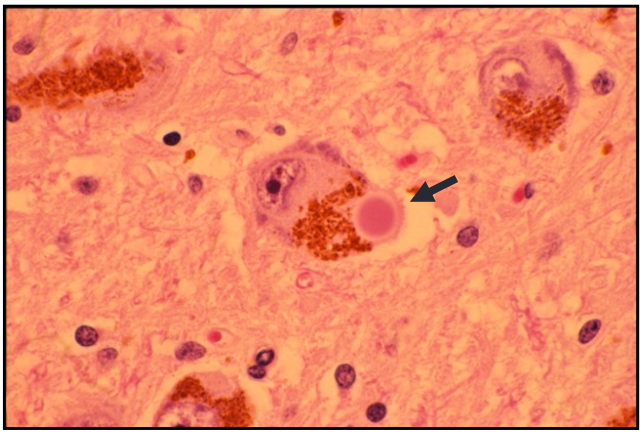
Pathology in Parkinson's Disease



H&E

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Lewy Body Pathology

- Mutations in ***alpha-synuclein*** gene linked to Parkinson's disease
- Duplications of alpha-synuclein gene linked to Parkinson's disease and dementia with Lewy bodies
- All Lewy bodies have alpha-synuclein protein
- Increased ability to detect Lewy body changes in brain studies

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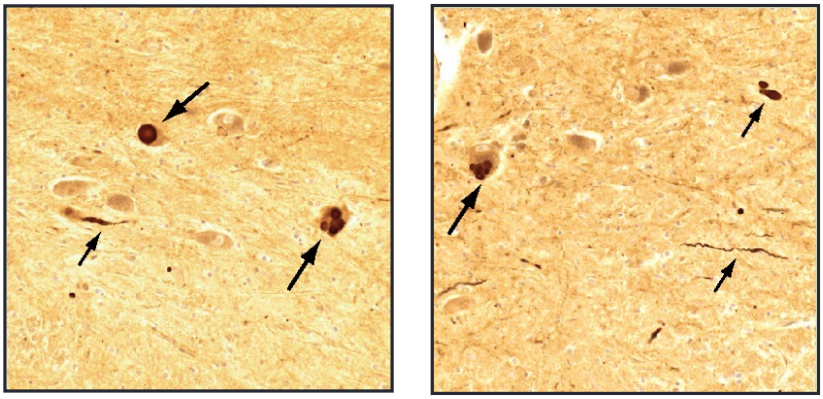
Pathology in Parkinson's Disease



α-synuclein immunohistochemistry

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Lewy Body Dementias

- 1.4 Million Americans
  - DLB, PDD, and LBV-AD
- Clinical care
  - Multiple visits before diagnosis, misdiagnosis
  - Inappropriate care (e.g., antipsychotics)
  - Patient and family distress
  - Access to long term care

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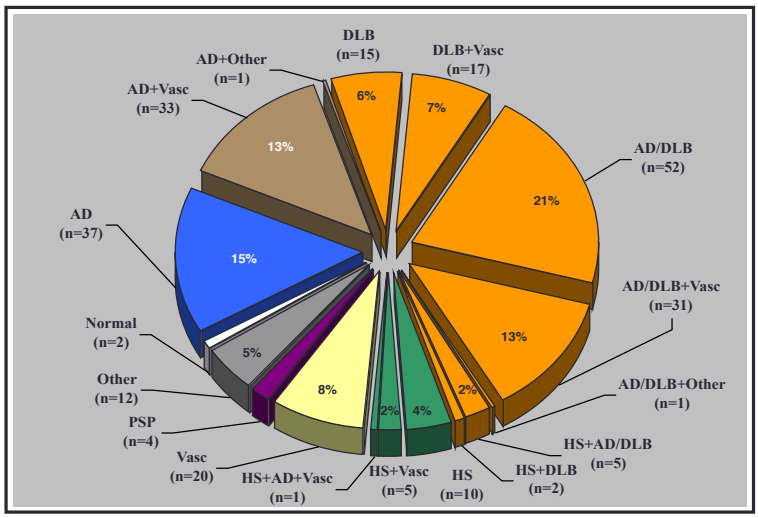
Neuropathology of Community Based Dementia



Leverenz et al, JAMA Neurol, 2002; Riekse et al JAGS, 2004; Leverenz et al, Brain Path, 2008

Lewy Body Dementias

- 1.4 Million Americans
  - DLB, PDD, and LBV-AD
- Clinical care
  - Multiple visits before diagnosis, misdiagnosis
  - Inappropriate care (e.g., antipsychotics)
  - Patient and family distress
  - Access to long term care
- Research
  - Consistent and coordinated research and funding (DLBC)

The Lewy Body Dementias

Parkinson's Disease Dementia

Dementia with Lewy Bodies

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Clinical Diagnosis of PD Dementia

2007 Clinical Diagnostic Criteria

- Diagnosis of PD
- Dementia syndrome within the context of established PD
  - » impairment in more than one cognitive domain
  - » decline from premorbid level
  - » deficits severe enough to impair daily life

Emre M et al, Mov Disord, 1689-1707, 2007.

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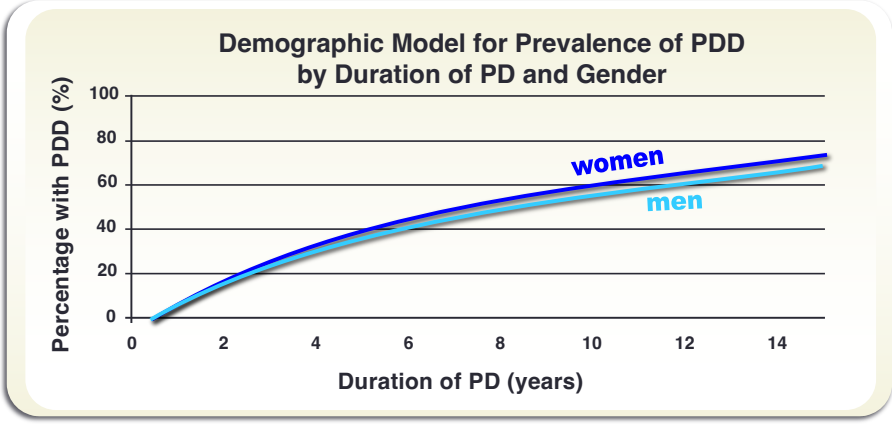
Dementia in Parkinson's Disease



Aarsland et al, JAMA Neurol, 2003.

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Cognitive Impairment is Common in Early PD

Table 1 Characteristics of incident Parkinson disease (PD) patients with and without mild cognitive impairment (MCI)

	Healthy controls*	All patients	PD-no MCI	PD-MCI
No.	171	196	159	37
Male, n (%)	102 (59.6)	115 (58.7)	94 (59.1)	21 (56.8)
Age at testing, y	67.3 (9.0)	67.6 (9.2)	67.0 (9.4)	70.2 (7.6)
Disease duration, y	NA	2.3 (1.8)	2.3 (1.7)	2.4 (2.1)
UPDRS motor subscore	NA	22.8 (11.1)	22.4 (10.9)	27.7 (12.2)
Education, y	11.7 (3.4)	11.0 (3.3)	10.9 (3.2)	11.2 (3.7)
MMSE	28.6 (1.5)	27.9 (2.3)†	28.2 (1.8)	26.5 (3.4)†
MADRS	1.2 (2.5)	4.2 (4.3)†	4.2 (4.3)	4.0 (4.4)
IQCode	3.06 (0.10)	3.14 (0.18)†	3.13 (0.18)	3.18 (0.2)
UPDRS item 1	NA	0.3 (0.5)	0.3 (0.5)	0.4 (0.6)†
Antidepressants, n (%)	4 (2.3)	24 (12.2)§	19 (11.9)	5 (13.5)
Sedatives, n (%)	8 (4.7)	23 (11.7)§	19 (11.9)	4 (10.8)

19%

Aarsland et al, Neurology, 1121-1126, 2009.

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Cognitive Impairment is Common in Early PD

"These findings highlight cognitive impairment as a key feature from the time of diagnosis of PD"

Aarsland et al, Neurology, 1121-1126, 2009.

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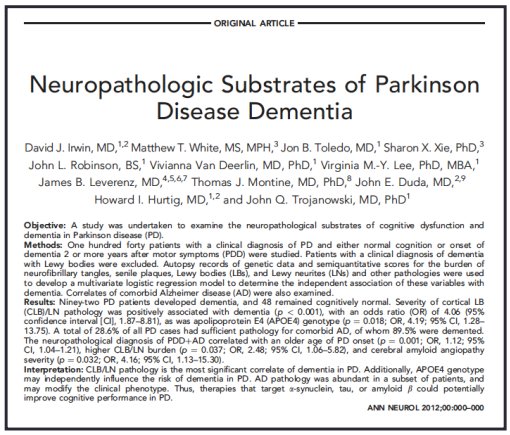
Pathology of Parkinson's Disease Dementia



ORIGINAL ARTICLE

Neuropathologic Substrates of Parkinson Disease Dementia

David J. Irwin, MD,[1,2] Matthew T. White, MS, MPH,[3] Jon B. Toledo, MD,[1] Sharon X. Xie, PhD,[3] John L. Robinson, BS,[1] Vivianna Van Deerlin, MD, PhD,[1] Virginia M.-Y. Lee, PhD, MBA,[1] James B. Leverenz, MD,[4,5,6,7] Thomas J. Montine, MD, PhD,[8] John E. Duda, MD,[2,9] Howard I. Hurtig, MD,[1,2] and John Q. Trojanowski, MD, PhD[1]

Objective: A study was undertaken to examine the neuropathological substrates of cognitive dysfunction and dementia in Parkinson disease (PD).
Methods: One hundred forty patients with a clinical diagnosis of PD and either normal cognition or onset of dementia 2 or more years after motor symptoms (PDD) were studied. Patients with a clinical diagnosis of dementia with Lewy bodies were excluded. Autopsy records of genetic data and semiquantitative scores for the burden of neurofibrillary tangles, senile plaques, Lewy bodies (LBs), and Lewy neurites (LNs) and other pathologies were used to develop a multivariate logistic regression model to determine the independent association of these variables with dementia. Correlates of comorbid Alzheimer disease (AD) were also examined.
Results: Ninety-two PD patients developed dementia, and 48 remained cognitively normal. Severity of cortical LB (CLB)/LN pathology was positively associated with dementia ($p < 0.001$), with an odds ratio (OR) of 4.06 (95% confidence interval [CI], 1.87–8.81), as was apolipoprotein E4 (APOE4) genotype ($p = 0.018$; OR, 4.19; 95% CI, 1.28–13.75). A total of 28.6% of all PD cases had sufficient pathology for comorbid AD, of whom 89.5% were demented. The neuropathological diagnosis of PDD+AD correlated with an older age of PD onset ($p = 0.001$; OR, 1.12; 95% CI, 1.04–1.21), higher CLB/LN burden ($p = 0.037$; OR, 2.48; 95% CI, 1.06–5.82), and cerebral amyloid angiopathy severity ($p = 0.032$; OR, 4.16; 95% CI, 1.13–15.30).
Interpretation: CLB/LN pathology is the most significant correlate of dementia in PD. Additionally, APOE4 genotype may independently influence the risk of dementia in PD. AD pathology was abundant in a subset of patients, and may modify the clinical phenotype. Thus, therapies that target α-synuclein, tau, or amyloid β could potentially improve cognitive performance in PD.

ANN NEUROL 2012;00:000–000

- **140 autopsied cases**
- **Links to dementia**
  - **Lewy pathology**
  - ***APOE ε4***
  - **AD (~ 30%)**

Irwin DJ, et al. Ann Neurol 2012

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Consensus Criteria for Dementia with Lewy Bodies

1. Dementia
2. Core features (2 = "probable", 1 = "possible")
   a. fluctuating cognition, attention, alertness
   b. recurrent visual hallucinations
   c. spontaneous features of parkinsonism
   d. *REM sleep behavior disorder*
3. *Indicative Biomarkers* (plus one core = "probable" DLB)
   a. Low dopamine transporter uptake (PET/SPECT)
   b. Abnormal MIBG myocardial scintigraphy
   c. PSG confirmation of RBD
4. **One year rule for PDD vs. DLB**

McKeith et al, Neurology, 2017.

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PDD vs. DLB

- Common clinical symptoms
  - Parkinsonism
  - Visual hallucinations
  - Fluctuations
  - REM Sleep Disorder
- Is it all timing
  - For criteria, yes
- Just a variant of same disease?

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The Lewy Body Dementias

Parkinson's Disease Dementia

Dementia with Lewy Bodies

Lewy Bodies and Alzheimer's Disease

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Lewy and Alzheimer

Frederick Lewy

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Lewy Body Pathology in Alzheimer's Disease

- High frequency in AD
  - Using ASN immunohistochemistry and amygdala sampling
  - 63% PS-1/APP mutation AD
  - 50% of Down syndrome
  - 61% of "sporadic" AD
  - 64% PS-2 mutation AD

Leverenz et al, Arch Neurol, 1986; Ditter et al, Neurology, 1987; Hamilton, Brain Path, 2000, Lippa, Lippa et al, AJP, 1998; Lippa et al Ann Neurol, 1999; Leverenz et al, Arch Neurol, 2006

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The Lewy Body Dementias

Symptoms

Parkinson's Disease Dementia

Dementia with Lewy Bodies

Lewy Bodies and Alzheimer's Disease

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Signs and Symptoms of the Lewy Body Dementias

Early Stage	*Middle Stage*	*Advanced Stage*
memory loss	→	→
executive dysfunction	→	→
apathy	→	→
depression	→	→
poor insight	*poor insight* →	→
cortical dysfunction	cortical dysfunction	cortical dysfunction
visual spatial	→	→
disruptive agitation	*disruptive agitation* →	→
psychosis	***psychosis*** →	→

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Formed Visual Hallucinations

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Sleep - RBD

- ***REM Sleep Behavior Disorder (RBD)***
  - strongly associated with Lewy body pathology
  - "acting out dreams"
  - responds to clonazepam, melatonin
- *Other sleep disturbance*
  - excessive daytime sleepiness
  - sleep apnea, periodic leg movments, restless leg
- *Frequently more than one disorder*

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Laboratory Testing

- ***Neuropsychology***
- ***Blood***
  - CBC, chemistry, TSH
  - B12, folate
  - Syphilis serology
  - Genetic testing*
- ***Cerebrospinal fluid***
  - **Aβ, tau, p-tau**
- ***Imaging***
  - **Dopamine Transporter (DAT Scan)**
  - **FDG-PET**
  - **MIBG cardiac imaging** (sympathetic innervation)
  - Structural (CT, MRI with hippocampal volume)

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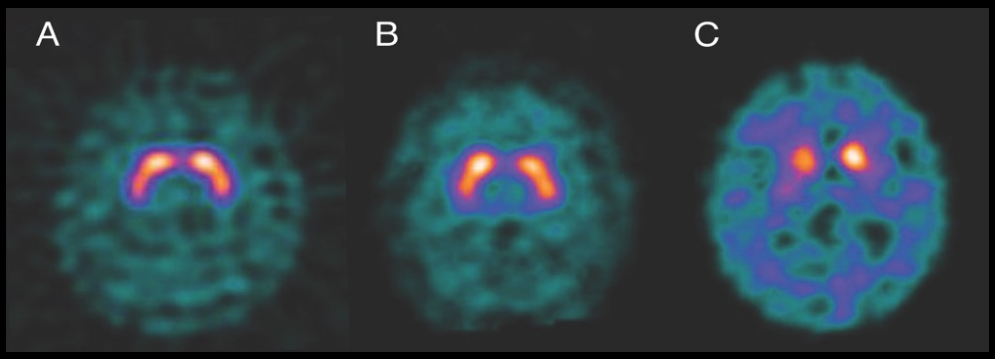
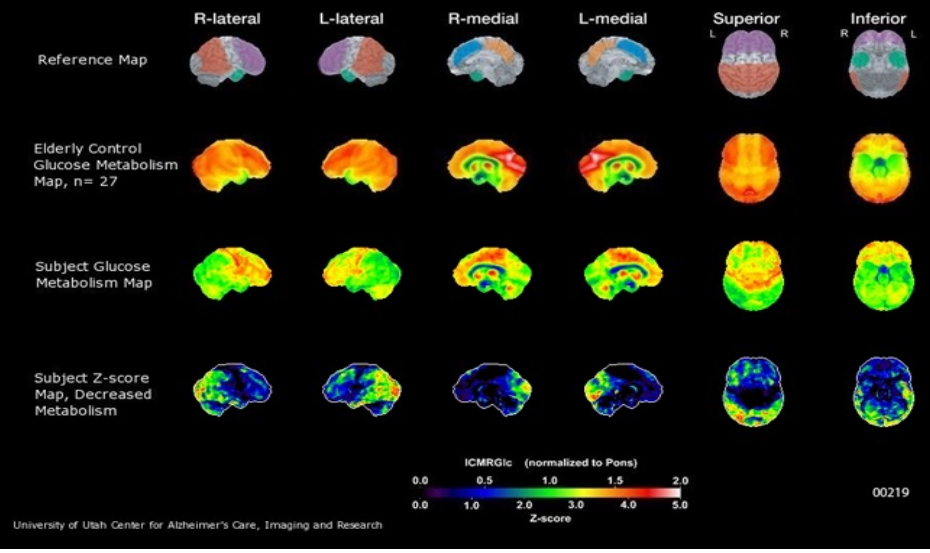
Dopamine Imaging in DLB/PD/PDD

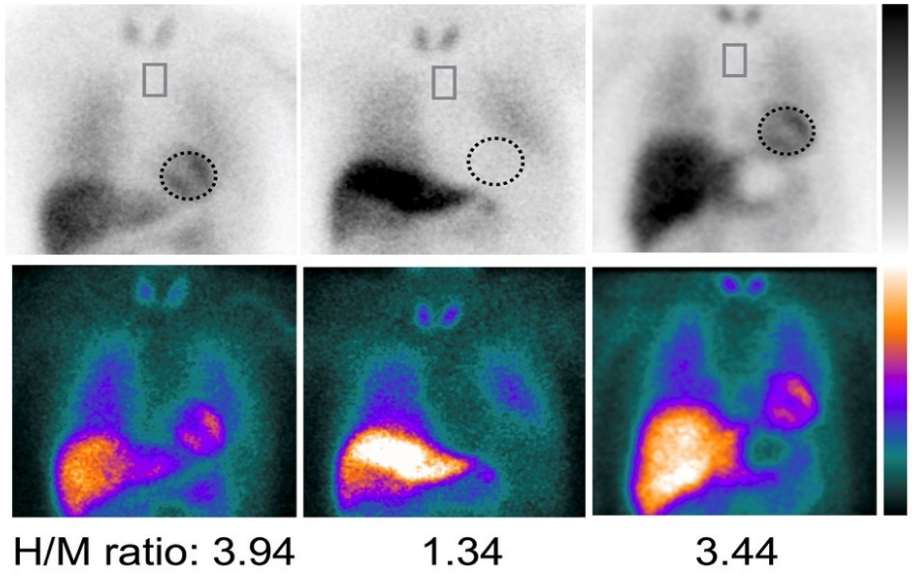


Cognitively normal	83 y.o. probable AD	81 y.o. probable DLB

Foster NL Neuroimaging in Weiner and Lipton., 2009: p. 105-136.

DLB/PDD





Nakajima et al, J Nucl Cardiol, 2014

ANNALS of Clinical and Translational Neurology
Open Access

BRIEF COMMUNICATION

Alpha-synuclein RT-QuIC in the CSF of patients with alpha-synucleinopathies

Graham Fairfoul[1], Lynne I. McGuire[1], Suvankar Pal[1,2], James W. Ironside[1], Juliane Neumann[3], Sharon Christie[4], Catherine Joachim[4], Margaret Esiri[4], Samuel G. Evetts[3], Michal Rolinski[3], Fahd Baig[3], Claudio Ruffmann[3], Richard Wade-Martins[5], Michele T. M. Hu[3], Laura Parkkinen[3] & Alison J. E. Green[1]

Groveman et al. Acta Neuropathologica Communications (2018) 6:7
DOI 10.1186/s40478-018-0508-2

Acta Neuropathologica Communications

METHODOLOGY ARTICLE Open Access

Rapid and ultra-sensitive quantitation of disease-associated α-synuclein seeds in brain and cerebrospinal fluid by αSyn RT-QuIC

Bradley R. Groveman[1†], Christina D. Orrú[1†], Andrew G. Hughson[1], Lynne D. Raymond[1], Gianluigi Zanusso[2], Bernardino Ghetti[3], Katrina J. Campbell[1], Jiri Safar[4], Douglas Galasko[5*] and Byron Caughey[1*]

Fairfoul G et al, *Ann Clin Transl Neurol*, 3:812-18, 2016
Groveman BR et al, *Acta Neuropath Comm*, 2018

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Treating the Lewy Body Dementias

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Current Therapies

Target	Therapy	Outcomes	Approval
Cognition	AChEi Memantine	+ +/-	+ (Japan only)
Behavior	Antipsychotic (quetiapine, clozapine, pimavanserin)	+/-	No
Sleep	Clonazepam Melatonin	+ +	No
Mood	SSRI TCAs	? ?	No

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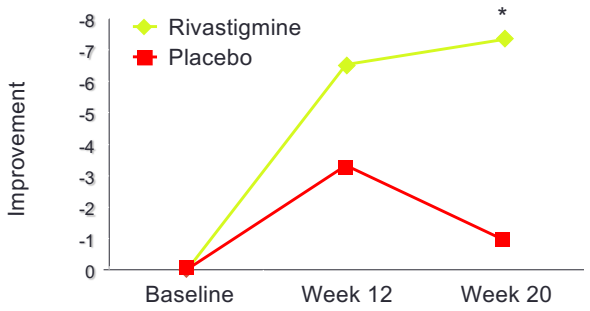
Rivastigmine International Lewy Body Dementia Trial: Behavioural Changes (NPI)

NPI 10-item Score–Mean Change from Baseline (OC)



*P<0.01 vs placebo (ANOVA/ANCOVA)
McKeith IG, et al. American Academy of Neurology 52nd Annual Meeting. April 29-May 6, 2000.
Mckeith IG et al, Lancet, 2000.

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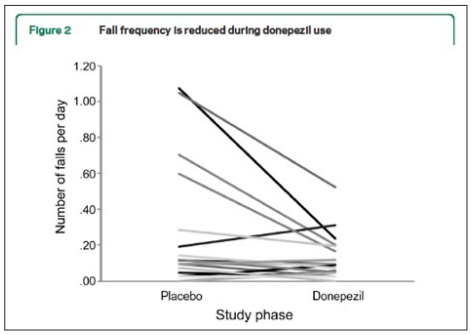
Other Benefits of Cholinergic Rx?



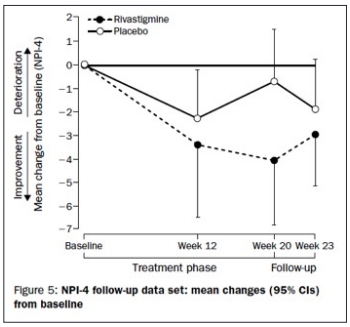


Figure 5: **NPI-4 follow-up data set: mean changes (95% CIs) from baseline**

Chung KA et al, Neurology, 2010. McKeith I et al, Lancet, 2000.

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"Biomarkers for the Lewy Body Dementias"
RFA-NS-16-022

- **Five Sites Funded**
  - ***"Dementia with Lewy Bodies Consortium" (CCF +8)***
  - "Lewy Body Dementia Biomarkers" (Frey, UM)
  - "Targeting Lewy Body Specific Pathology Using Biomarkers" (Marder/Honig, Columbia U)
  - "GBA pathway markers for Lewy body dementia" (Scherzer, Harvard U)
  - Mayo Clinic (Boeve/Kantarci)

DLBC
Dementia with Lewy Bodies Consortium

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National Alzheimer's Project ACT
2016 Lewy Body Dementias Recommendations

1. Initiate clinical trials for motor and non-motor manifestations of LBD
2. ***Create longitudinal clinical, biological, and imaging resources for LBD***
3. Characterize disease-specific changes in brain and other tissues
4. Identify common and novel gene variants, epigenetic changes, environmental influences
5. Develop imaging approaches to enhance diagnosis, detect latent/prodromal disease, and monitor progression
6. **Develop biomarkers (using samples from recommendation 2)**
7. Develop animal, cellular, in vitro models for synucleiopathies
8. Develop disease modifying therapies

"Biomarkers for the Lewy Body Dementias"
RFA-NS-16-022

- ***Expand the collection of clinical data and biologic specimens in the NINDS PDBP to include patients with LBD***
- ***Support hypothesis-driven clinical research to discover biomarkers that will improve efficiency and outcome of Phase II clinical trials for LBD***

Dementia with Lewy Bodies Consortium

- Ten Centers with extensive LBD experience
  - All members of the LBDA Scientific Advisory Council
  - Cleveland Clinic coordinating site
  - LBDA support for annual meetings
- Focus on developing a longitudinal study sample with compatibility with multiple programs:
  - Parkinson's Disease Biomarker Program (NINDS)
  - National Alzheimer's Center program (NIA)
  - Alzheimer's Disease Neuroimaging Initiative (NIA)

DLBC
Dementia with Lewy Bodies Consortium

Questions?

DLBC
Dementia with Lewy Bodies Consortium

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Cleveland Alzheimer's Disease Research Center

2022 Expert Briefings

Expert Briefings
Parkinson's Foundation

Wednesday, February 2

Sights, Sounds and Parkinson's
Ali G. Hamedani, MD, MHS

Wednesday, March 2

Conversations About Complementary Therapies and PD
Nitai D. Raz, MD

Wednesday, April 6

Can We Put the Brakes on PD Progression?
Joanne Wojcieszek, MD

Wednesday, September 7

The Impact of Physical Activity in PD
Miriam Rafferty, PT, DPT, PhD

Wednesday, November 2

Let's Talk About Dementia
James Leverenz, MD

SEE YOU IN 2023!

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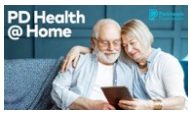
Resources and Support

Aware in Care
Parkinson.org/AwareInCare

PD Library
Parkinson.org/PDLibrary



PD Health @ Home
Parkinson.org/PDHealth

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Resource and Support Continued

Podcast: Substantial Matters
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Professional Education
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PD Generation
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We're Here For You

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Before You Go…

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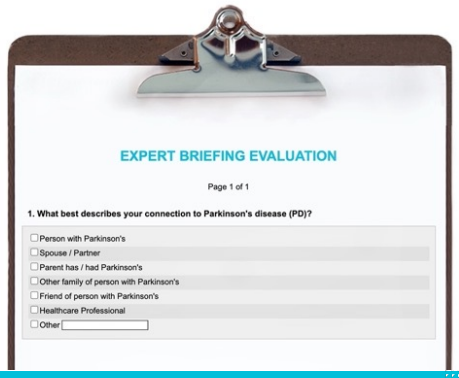
Your feedback is important to us!
Please complete the evaluation after the close of this webinar.



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