

# LEWY BODY DEMENTIA: THE STATE OF THE SCIENCE



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# LEWY BODY DEMENTIA THE STATE OF THE SCIENCE

## A Letter from the CEO

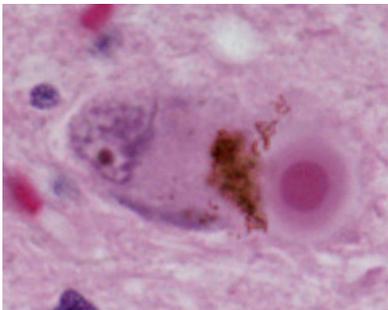
We are entering an era of unprecedented opportunity for understanding and treating Lewy body dementia (LBD). First described 40 years ago, LBD is now recognized to be among the top three causes of dementia in the U.S. and worldwide. Nonetheless, research (and its funding) has lagged far behind Alzheimer's disease (AD) and other common age-related dementias. As a result, progress has been relatively slow to date in unraveling the biological causes of LBD and improving our ability to diagnose and treat the disorder.

Things are changing now as a result of three key developments. First, epidemiological studies have revealed that LBD ranks, together with Alzheimer's disease and cerebrovascular disease, as a major cause of dementia in the aged. Second, because LBD shares clinical features and biological causes with both AD and Parkinson's disease (PD), research studies in these three disorders will be mutually synergistic. Third, the National Alzheimer's Project Act (NAPA), enacted by President Obama in 2011 to create a strategic plan to rid the nation of Alzheimer's disease, mandated also addressing LBD and other forms of dementia.

As a result of these developments, awareness of LBD as a key public health priority is dramatically rising, resulting in historic actions:

- For the first time, the scientific community developed a national LBD research strategy, with input from LBDA and LBD patient advocates, as one of the deliverables of the National Institutes of Health (NIH) Alzheimer's Disease-Related Dementias research summits. (The published recommendations can be accessed at [europepmc.org/articles/pmc4155046](https://europepmc.org/articles/pmc4155046).)

- A dramatic increase was made in dementia research funding in the fiscal year 2016 federal budget, due to a new federal law mandating NIH submit an annual ‘professional judgment’ budget to Congress for funding Alzheimer’s and related dementia research strategies.
- NIH is now soliciting and funding research proposals to help achieve key research milestones in the LBD research strategy.



We know how important LBD research is to the LBD families we support, and we at the Lewy Body Dementia Association are thrilled about the gains made in LBD research and advocacy in the last 5 years. Therefore, LBDA is publishing, “Lewy Body Dementia: The State of the Science,” to update the LBD community with the major findings to date in LBD research. While this paper does not purport to be an exhaustive, scientifically detailed review of the field, it highlights the vast array of opportunities driving research progress.

Together with LBD experts in academic centers, representatives from federal agencies, foundations and for profit corporations, and most importantly, the LBD community itself, LBDA is committed to eliminating barriers hindering LBD research and opening up avenues for new exploration and advancement.

We hope you will join us in this scientific journey as a vital stakeholder in LBD research!

Sincerely,  
Todd C. Graham  
Executive Director  
Lewy Body Dementia Association

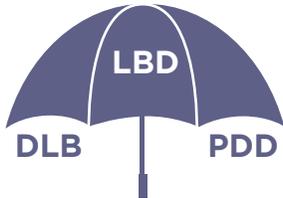
Mark Wall  
Executive Director  
Lewy Body Dementia Association

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# The Lewy Body Dementia Spectrum



Full 2013 recommendations are available in the appendix of the published summit report, found at [europepmc.org/articles/pmc4155046](http://europepmc.org/articles/pmc4155046).

Updates to recommendations were presented at the 2016 ADRD Summit; a final report is expected later this year. This research strategy serves as a platform upon which all LBD stakeholders can build new research initiatives and collaborations to fill knowledge gaps and achieve key scientific advances.

LBD is an umbrella term that includes two clinical diagnoses: “dementia with Lewy bodies” (DLB) and “Parkinson’s disease dementia” (PDD). These disorders share a common biological disease process, but have differing primary symptoms in the early stage. In order to more fully understand the differences and commonalities of these two disorders, research is needed on each disorder, as well as collectively on the spectrum of Lewy body dementias.

In 2013 the National Institutes of Health (NIH) organized the Alzheimer’s Disease-Related Dementias Summit (ADRD Summit) to present draft research recommendations for Lewy body dementias, as well as vascular, mixed, and frontotemporal dementias. Stakeholder feedback to the draft recommendations, including patient advocates and representatives from LBDA, were incorporated into the final report. This was the first national research strategy ever developed for LBD.

## ADRD Summit: 2013 Recommendations for LBD Research

1. Establish longitudinal patient cohorts (i.e., recruit groups of patient volunteers who can be followed over time) for LBD research studies and clinical trials.
2. Create clinical, biological and imaging resources to study these cohorts from the earliest stages of disease to autopsy, with the goals of improving the accuracy of detection and diagnosis of LBD and defining biological changes occurring in people with LBD.
3. Discover disease mechanisms in LBD by:
  - a. Systematically mapping disease-specific changes in the brain, spinal cord, and peripheral nervous system with state-of-the-art methods, including genomics, gene expression analyses, and profiling of tissue and fluid metabolites and proteins.
  - b. Identifying new genetic variants, epigenetic changes (long-term alterations in gene expression), and environmental factors that influence the risk and clinical features of LBD.
4. Identify and validate biomarkers for LBD, including both changes in brain structure and blood and tissue levels of specific biomolecules.
5. Develop new treatments for LBD based on research discoveries.

# THIS REPORT FOCUSES ON DLB ►

## Terminology

*Disease names and other terminology in the dementia field can be confusing. Here are some key terms used in this report:*

**Dementia with Lewy bodies (DLB):** A progressive neurological disorder affecting thinking, movement, behavior, sleep, and the autonomic nervous system. Most often misdiagnosed as Alzheimer’s disease.

**Parkinson’s disease dementia (PDD):** The clinical diagnosis made when cognitive impairment progresses to dementia in a person already diagnosed with Parkinson’s disease.

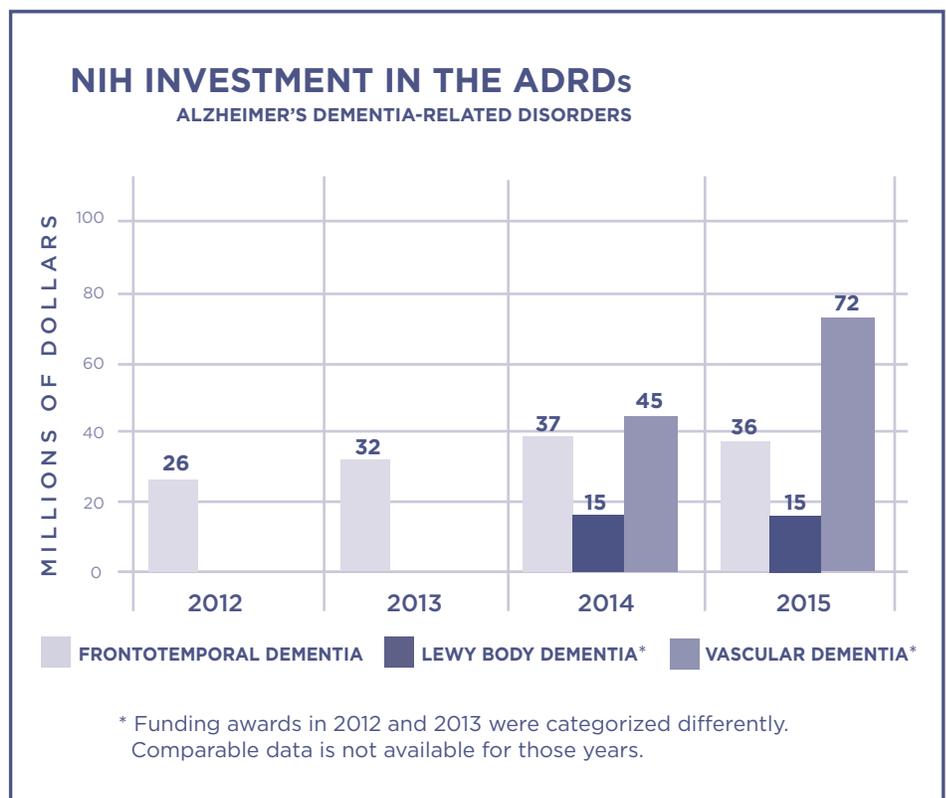
**Lewy body dementia (LBD):** An umbrella term that includes both DLB and PDD, because both disorders are characterized by Lewy body pathology. Both disorders eventually involve motor as well as cognitive symptoms. However, in PDD motor symptoms appear first in the early stage, whereas in DLB cognitive symptoms appear first and predominate.

**Dementia:** A loss of cognitive abilities serious enough to interfere with a person’s day-to-day functions.

**Mild cognitive impairment (MCI):** A modest decline in cognitive abilities that is not sufficiently severe to interfere significantly with day-to-day functions.

## Taking Aim at Dementia with Lewy Bodies

Both DLB and PDD are very under-studied, in comparison to AD. However, the increasing recognition of dementia as a common complication of PD has led to increasing study of PDD through the relatively well-funded PD research programs. In contrast, systematic study of DLB has been very difficult. In part, this is due to people with DLB being difficult to diagnosis as they may not show typical symptoms other than dementia early in the course of the disease (e.g., motor symptoms of parkinsonism, visual hallucinations) and thus their cognitive impairment may be wrongly attributed to AD. Significantly, this led to essentially no large-scale studies of DLB, a lack of research funding focused on DLB, and as a result, the field is hindered by substantial research gaps.



Source: [https://report.nih.gov/categorical\\_spending.aspx](https://report.nih.gov/categorical_spending.aspx)

# What is DLB?

**DLB is a common form of age-related dementia.** Its name comes from the underlying biological disease process, the accumulation of Lewy bodies in brain cells. These are abnormal clumps, named after the doctor who first identified them, of a protein called alpha-synuclein.

The central characteristic of DLB is a progressive loss of cognitive function that significantly interferes with everyday life (dementia). Compared to patients with AD, those with DLB tend to have more severe problems with visual processing as well as executive function (the ability to plan and carry out actions). Memory, while impaired, is relatively intact in comparison to AD, which commonly presents with prominent short term memory impairment (difficulty remembering recent events, conversations, etc.).

Other core features of DLB include unpredictable changes in cognition and attention (fluctuations), impairments in motor function typical of Parkinson's disease (parkinsonism), visual hallucinations, rapid eye movement (REM) sleep behavior disorder (in which a person physically acts out his or her dreams), and problems with automated, more basic body functions like blood pressure, temperature regulation and digestion and urinary control.

DLB is usually diagnosed by a specialist in neurology, psychiatry or geriatrics after taking a person's medical history, doing blood tests and a brain image (e.g., MRI) to rule out other medical causes, performing a neurological exam, and doing a mental status test. The profile of impairments on neuropsychological tests can also be helpful in making the DLB diagnosis. These are more extensive cognitive tests that can identify areas of decline in different cognitive skills, such as the level of relative impairments of memory versus language or planning skills.

As is the case for other age-related neurodegenerative diseases, there is currently no "cure" for DLB and no way to halt its progression. Importantly, though, treatments are available to address many of the symptoms of the disorder.<sup>1</sup> This can improve quality of life for both the person with DLB and caregivers. These treatments, however, have all been developed for other disorders, including AD, PD, and psychiatric conditions. At this time there are no drugs that

have been specifically approved by the United States Food and Drug Administration (FDA) for the treatment of DLB symptoms.

These treatments include acetylcholinesterase inhibitors (to improve cognition), anxiolytics and antidepressants (for anxiety and depression), and melatonin or other sleep medications (for REM sleep behavior disorder). Autonomic symptoms can be treated with non-pharmacological treatments as well as drugs (e.g., increasing dietary salt to improve hypotension, and dietary fiber for constipation).

For additional information on the symptoms and treatment of DLB, visit [LBDA.ORG](http://LBDA.ORG).

Of course, drug treatment regimens must be used with great care to minimize potential adverse side effects. DLB patients, in particular, are extremely sensitive to certain neuroleptic (antipsychotic) medications sometimes used to treat behavioral symptoms in dementia. In certain situations, some physicians may carefully use the lowest effective dose of this class of medications to manage disturbing hallucinations or severe agitation in DLB if non-pharmacologic treatments are not effective and there is a potential safety issue from the behavioral symptoms.■

# Prevalence

Recent estimates suggest that DLB is responsible for 4 to 16% of cases of dementia seen in the clinic.<sup>2</sup> The true prevalence of DLB is probably higher. DLB can be challenging to diagnose, and many primary care physicians are not trained to recognize DLB or to distinguish it from AD.

Currently, the only way to diagnose DLB definitively is by identifying Lewy bodies in a patient's brain tissue after death. Careful autopsy studies suggest that many people diagnosed clinically with AD while alive actually have DLB,<sup>3</sup> and that DLB accounts for 10 to 25% of cases of dementia.<sup>3, 4</sup>

Part of the difficulty in establishing accurate prevalence data for DLB is that many patients with DLB also show signs of AD at autopsy. Up to 70% of autopsy-confirmed DLB cases have moderate to high levels of AD neuropathology, and Lewy body pathology is found in up to 50% of all cases of autopsy-confirmed AD.<sup>5, 6</sup>

## Future Directions

Gathering accurate data on DLB prevalence is important for raising awareness about the disorder among health care providers and the general public, and making sure that people with DLB are diagnosed correctly and receive proper treatment. Community-based epidemiology studies are needed.

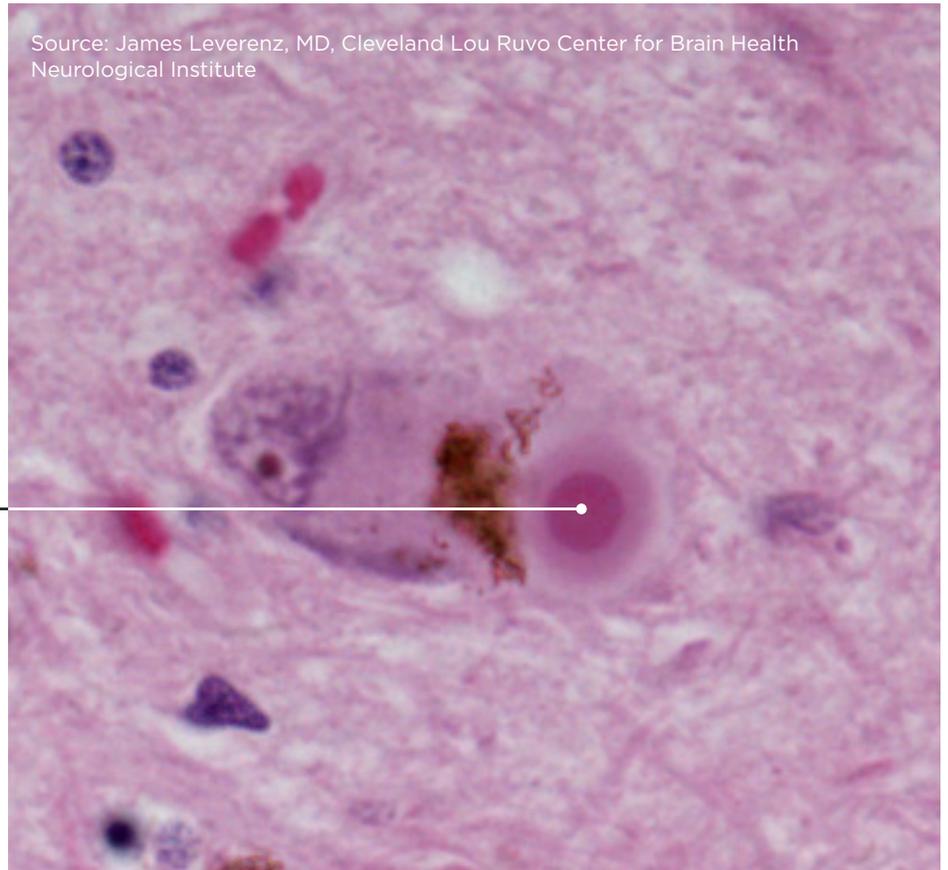
Currently, there is no national patient registry for DLB. However, some individuals with DLB are included in longitudinal studies carried out by some NIH-funded Alzheimer's Disease Research Centers.

Another key question for future research is how DLB prevalence varies in different populations. DLB appears to be more common among men than women.<sup>7, 8</sup> Learning more about how race, gender and socioeconomic factors affect risk of DLB will improve outreach to at-risk populations, and also provide insights into how different genetic and lifestyle factors contribute to the disorder.■

# The Biology of DLB

DLB is associated with protein misfolding. Alpha-synuclein is a type of protein present in everyone's brain. The normal function of alpha-synuclein in nerve cells is not yet fully understood. It is known to be abundant in nerve cell processes in both the brain and other organs of the body. It appears to be involved in the regulation of the release of chemical messengers (neurotransmitters) from nerve cell processes. Like other proteins, alpha-synuclein is

Source: James Leverenz, MD, Cleveland Lou Ruvo Center for Brain Health Neurological Institute



The Lewy body is visible under the microscope at autopsy when a special staining technique is used on brain tissue.

produced in cells as a string of amino acid building blocks. These must then fold into a specific three-dimensional shape in order to function properly. Genetic mutations or cellular stressors can cause alpha-synuclein molecules to fold into abnormal shapes and stick to one another. With time, these sticky protein aggregates build up inside cells like hairs caught in a drain, eventually forming the round clumps called Lewy bodies that are visible under the microscope at autopsy. At various stages during their aggregation, the abnormally folded alpha-synuclein deposits interfere with cellular function, and eventually cause cell death.<sup>9</sup>

## Mechanisms of Disease Progression

The aggregation of misfolded alpha-synuclein occurs in stages. First, a few misfolded molecules clump to form small complexes called “oligomers.” The oligomers then stick together into fibrils, which then aggregate into larger clumps and eventually into Lewy bodies.

It is theorized that the spread of alpha-synuclein pathology through the brain proceeds like dominoes falling.

Misfolded alpha-synuclein molecules provoke nearby normal alpha-synuclein molecules into adopting their abnormal configuration and sticking to them. Recent data suggest that the misfolded alpha-synuclein proteins may spread from one cell to a neighboring cell, causing normal alpha-synuclein molecules in the next cell to misfold, and then further spread the disease through the brain. (This line of work requires much more research to characterize the biological process better.) There is no evidence that DLB can be transmitted between individuals.<sup>10</sup>

The brains of people with DLB also usually contain amyloid plaques and neurofibrillary tangles (the signature pathologic features of AD) in addition to Lewy bodies.<sup>11</sup> Like Lewy bodies, plaques and tangles are aggregates of abnormally folded proteins (amyloid beta-42 and tau, respectively). People whose brains contain plaques and tangles in addition to Lewy bodies tend to show more rapid cognitive decline than those with Lewy bodies or AD alone.<sup>12, 13</sup> DLB may also be accelerated or worsened by cerebrovascular disease,<sup>14, 15</sup> which is common in older people.

## Brain Regions and Processes Affected in DLB

For reasons still not clear to scientists, some populations of neurons are more prone to develop Lewy bodies than others. Lewy bodies typically develop first in the olfactory bulb (a brain structure above the roof of the nasal cavity, involved in processing smells) and in neurons that send cell processes to the heart, gut, and other internal organs.<sup>16</sup> They also appear in the brain in certain regions important for thought and emotion, and other regions involved in movement and sleep.

The buildup of alpha-synuclein inside neurons interferes with their ability to generate electrical signals and release

Fortunately, neurons do not start dying until relatively late in the disease process, and their dysfunction is likely reversible if drugs can be found to stop the process of alpha-synuclein accumulation.

neurotransmitters, such as dopamine and acetylcholine.<sup>17, 18</sup> Abnormal alpha-synuclein deposits also provoke inflammatory responses in the brain, which further worsens brain function.<sup>19</sup>

## Future Directions

Scientists are still trying to understand what causes alpha-synuclein molecules to misfold and start sticking together in the first place. Genetic factors are one cause. Most cases of DLB do not run in families, but certain genes can increase one's risk for developing alpha-synuclein pathology. Normal processes of cellular aging, together with cellular stressors like environmental toxins and oxygen, are also believed to contribute to alpha-synuclein misfolding and aggregation.

The good news is that the accumulation of misfolded alpha-synuclein and its spread from cell to cell is a slow process that evolves over a period of years. Therefore, researchers are actively seeking drugs to intervene with these processes even after it has started.

Much of our understanding of the biology of DLB and other Lewy body disorders (PD and multiple system atrophy) has come from animal models, in which the animal has been genetically engineered to express mutant forms of alpha-synuclein. Existing animal models each have limitations in what they can reveal about the disease, and none perfectly replicates the symptoms seen in DLB. Therefore, scientists are also developing additional animal and cellular models that better mimic the human disease.

Ultimately, better understanding of the biology of DLB must be informed by human studies. In the past, these have been limited mostly to studies of clinical symptoms assessed at a single point during a patient's lifetime and cellular changes seen in their brains after death. Today, however, there are new technologies that can follow changes in brain structure, function, and biochemistry while patients are still alive. Such "longitudinal" studies may reveal new biomarkers for DLB. (Biomarkers are biological indicators that can be used to detect and predict the progress of a disease. Examples of biomarkers include specific proteins in the blood or spinal fluid, or

brain changes that can be detected by a variety of brain imaging methods.) Studies of biomarker changes can be combined with genetic analyses in people with DLB to provide a clearer picture of the biology of the disease.

Powerful longitudinal studies require large numbers of volunteers with DLB or people at risk of developing DLB. These studies also require research centers equipped to do cutting edge imaging scans, electroencephalography (EEG), cognitive assessments and other clinical tests. These resources enable researchers to collect biological fluids and brain samples at autopsy, and to carry out sophisticated data analyses.

Large studies in humans also require panels of expert scientists and health practitioners to organize and carry them out. One of the biggest barriers in DLB research in the U.S. today is lack of a formal research consortium dedicated to the study of DLB. Such a consortium is currently being organized in Europe, and could provide a model for future efforts elsewhere in the world.■

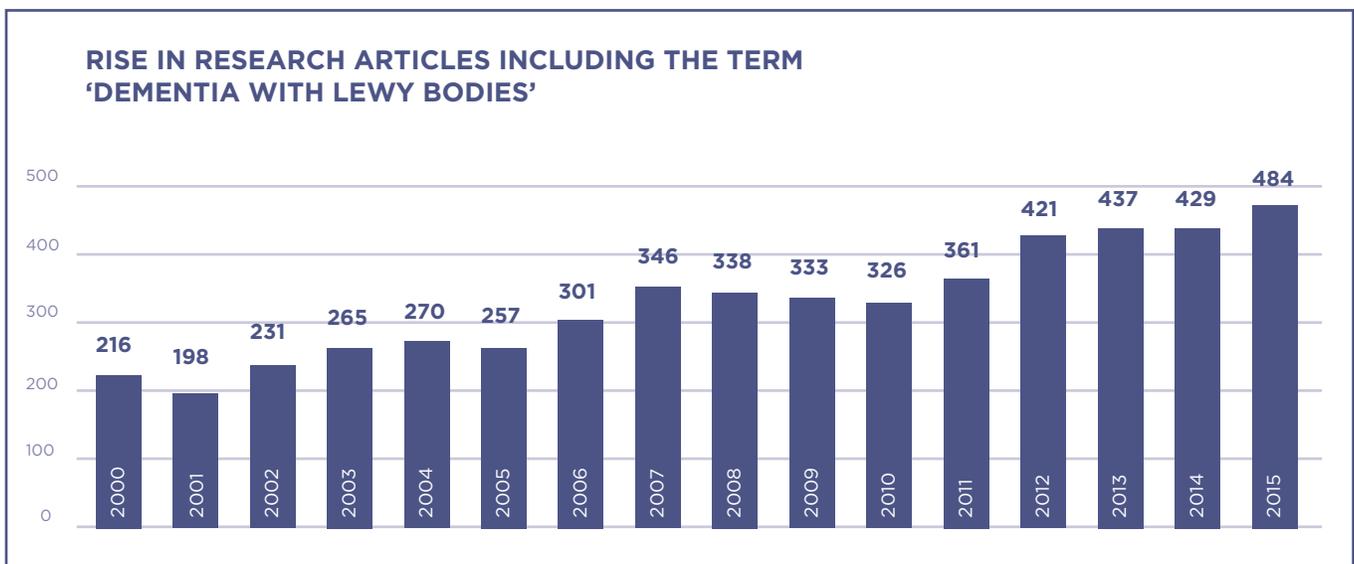
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# Diagnosis, Detection and Monitoring

Many of the symptoms of DLB can be treated, but patient safety due to severe medication sensitivities is a serious concern if the disorder is not correctly diagnosed in the first place. Accurate diagnosis is important not only for patient care, but also for patient-based studies of the biology of the disease and for clinical trials.

## Improving Accuracy of Diagnosis

It has only been 40 years since DLB was first identified and the criteria doctors use to diagnose it are still evolving. Currently, diagnosis is based on criteria



Source: Medline (PubMed) Trend

established by an expert panel in 2005.<sup>20</sup> (Updating the diagnostic criteria was a key area of discussion at the 2015 International DLB Conference in Ft. Lauderdale, FL. An updated set of diagnostic criteria is expected to be published later this year.)

In any disorder, the accuracy of diagnostic criteria depends in part on the sophistication of the diagnostic tools used to apply them. In various DLB research studies, the criteria have shown 79 to 100 percent specificity — that is, the criteria are very good at distinguishing DLB from other dementias.<sup>21</sup> In general the criteria have shown significantly poorer sensitivity (they fail to detect many cases of DLB) outside of specialty centers.

Part of the challenge in diagnosing DLB is that the patients with the disorder often present with different constellations of symptoms. A second problem is that

there are no standard procedures for health providers to use in applying the consensus diagnostic criteria in daily practice. Recently, a simple composite DLB risk test was developed that consists of 10 simple yes/no questions about symptoms. This test showed 94% sensitivity and 78% specificity in distinguishing between DLB and AD in its trial run,<sup>22</sup> but awaits validation by other researchers before it can be put into routine clinical use.

Yet another issue in diagnosing DLB is that many people with DLB also have co-existing Alzheimer's disease. This may result in symptoms of both disorders, making clinical diagnosis even more challenging.

### Earliest Stages of DLB

Like most neurodegenerative diseases, DLB develops gradually over a period of years or even decades. Ideally, drug treatments and/or lifestyle changes would be started as early in the disease process as early as possible, before serious symptoms appear.

Researchers have identified a number of early clinical signs that may ultimately help identify people at risk for DLB.<sup>23-25</sup> These symptoms can precede the emergence of dementia by years:

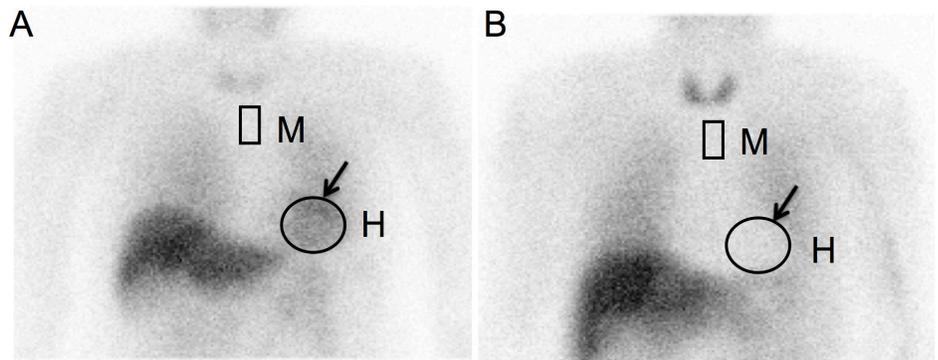
- REM sleep behavior disorder (RBD): almost all (over 80%) of patients with RBD later develop a synucleinopathy, with DLB and PD being by far the most common.<sup>26</sup>
- Anosmia (impaired sense of smell)<sup>27</sup>
- Impaired color vision
- Depression
- Autonomic dysfunction, including constipation, problems with bladder control, low blood pressure.

People who eventually develop DLB also first show milder cognitive symptoms.<sup>23, 24</sup> Researchers are now actively studying this pre-dementia stage of DLB (MCI-DLB) and developing new cognitive tests to detect it as early as possible.

### Biomarkers

Biomarkers aid physicians in diagnosing a disease and predicting its future course. They are also invaluable in tracking the effects of potential treatments for the disease.

MIBG scintigraphy scans compare a person with AD (A) to a person with DLB (B). This diagnostic technique compares the ratio of the tracer uptake into the heart (H), over the uptake in a section of chest space, the mediastinum (M). An abnormal scan indicates degeneration in the sympathetic nerve terminals in the heart, which is common in DLB but not AD.



Source: Masahito Yamada, Kanazawa University

## Imaging Biomarkers

DLB has a “diffuse” disease process: Lewy bodies and other degenerative changes occur in many, widely scattered regions of the brain. The brain structural changes in DLB are relatively subtle (compared to those in AD, for example), and MRI imaging is not particularly useful in diagnosing DLB. MRI is useful, however, in ruling out other potential causes of dementia in cases in which DLB is suspected.<sup>16</sup>

**Fluorodeoxyglucose positron emission tomography (FDG-PET)**, which measures regional use of glucose throughout the brain, is more useful. The brains of people with DLB may show decreased metabolism in the occipital lobe of the cortex, where visual information is processed.<sup>28</sup> FDG-PET scans have good sensitivity and specificity for detecting DLB.

Another useful, and very sensitive, method is imaging of midbrain dopamine transporter levels, done by **<sup>123</sup>Iodine-ioflupane SPECT (also called FP-CIT or the DaTscan)**.<sup>29</sup> While most individuals with DLB have dysfunction of midbrain dopamine neurons, in some people that dysfunction may not be prominent enough to be detected. Thus this method cannot identify absolutely everyone with DLB or the earlier stages of the disease.

Another promising tool is **<sup>123</sup>Iodine-metaiodobenzyl-guanidine myocardial (MIBG) scintigraphy**. In this technique, patients are injected with a radioactive tracer that binds to sympathetic nerve terminals in the heart. These nerve terminals degenerate in DLB, so there is less ‘labeling’ in the heart region in scintigraphy scans of DLB patients compared to healthy controls. The sensitivity and specificity of MIBG scintigraphy were 93% and 100%, respectively, in the hands of the Japanese researchers

who developed it,<sup>30</sup> and the technique is being further evaluated worldwide.

### Cerebrospinal Fluid (CSF) Biomarkers

Clinical research studies have shown that people with AD can be identified with a high degree of accuracy based on CSF levels of amyloid beta-42 and tau, two proteins known to play major roles in the development of AD. Similarly, alpha-synuclein is an obvious candidate CSF biomarker for DLB and other Lewy body disorders, and there is some evidence for changes in CSF alpha-synuclein in people with DLB.<sup>31</sup> Developing alpha-synuclein as a biomarker has been challenging as it is not yet clear which forms of the protein are the primary culprits in the disease. Scientists are currently tackling this problem by developing antibodies and other molecular probes that can distinguish between the various potentially toxic forms of alpha-synuclein.

### Electroencephalography (EEG) Biomarkers

The degeneration of specific brain circuits in DLB leads to changes in the brain's electrical firing patterns, which can be detected by EEG.<sup>32</sup> For example, the fluctuations in cognition experienced by DLB patients are accompanied by abnormal fluctuations in their EEGs.

### Future Directions

The ideal imaging biomarker for DLB will be one that identifies misfolded alpha-synuclein, and researchers are exploring compounds that can bind to alpha-synuclein so Lewy bodies can be visualized on brain scans.<sup>33, 34</sup> Other CSF biomarkers being explored include markers of brain inflammation and synaptic degeneration; blood biomarkers are also being sought. In addition, EEG offers great promise as a diagnostic tool because it is inexpensive and non-invasive, and can be easily done in most hospitals.

While scientists have identified numerous early symptoms and potential biomarkers for DLB, large longitudinal studies are needed to assess the predictive value of these markers. Currently, a standardized test battery specific to DLB is being developed that will allow federally-funded Alzheimer's Disease Research Centers across the U.S. to include more DLB patients in longitudinal studies and pool data in a large, public database.■

# Risk Factors and Prevention

## Genetic Risk Factors

DLB is usually a sporadic disorder — that is, it is not usually inherited directly from one generation to the next. Nonetheless, variations in the sequences of certain genes can increase a person’s risk of developing DLB.<sup>35, 36</sup> The genes most strongly implicated in DLB to date are:

- **SNCA**, the gene that “encodes” for the protein alpha-synuclein. (This means it includes the blueprint for where and how to produce alpha-synuclein.)
- **SCARB2**. This gene encodes lysosome membrane protein-2. (Lysosomes are bodies within cells that act as cellular waste disposals by digesting unwanted materials inside cells.)
- **GBA**: encodes another lysosomal protein, the enzyme  $\epsilon$ -glucocerebrosidase. (This enzyme processes certain fats, called glycolipids.)
- **APOE $\epsilon$ 4**. This variant of the gene for apolipoprotein E is the strongest known risk factor for AD. It is not yet clear if APOE $\epsilon$ 4 increases DLB risk by the same mechanisms that it increases AD risk (for example, by promoting amyloid plaque buildup) or different ones.

The gene variants associated with increased risk of DLB are relatively common: for example, about 14% of the general population carries the APOE $\epsilon$ 4 allele. However, possessing one of these gene variants does NOT indicate a person will develop DLB — only that one’s risk is increased.

Hereditary forms of DLB have been found only in rare circumstances, of patients with strong family histories of Lewy body disorders (i.e., multiple generations with multiple individuals with DLB or PD). Therefore, genetic testing is not included in routine clinical diagnosis of DLB. Those interested in seeking genetic testing should first consult a genetic counselor.

Variations in the SNCA and SCARB2 genes increase risk of PD as well as DLB. However, the variations associated with DLB are found in different regions of the two genes than the ones associated with PD.

Genome-wide association studies (GWAS) have revolutionized genetics, allowing researchers to take

a snapshot of an individual's complete set of DNA (or genome). GWAS studies found that DLB shares other genetic risk factors with both AD and PD, indicating that DLB shares some common biological mechanisms with each of the other two disorders.<sup>36</sup> Thus, improved understanding of the biology of DLB will likely provide new insights into AD and PD as well.

### Environmental/Lifestyle Risk Factors

Unlike genetic risk factors, some environmental and lifestyle factors that increase disease risk can in theory be changed relatively quickly. Unfortunately, as of this writing, only a handful of studies have looked at preventable risk factors for DLB. Those studies suggest that DLB risk is increased in people with histories of depression, anxiety, or stroke, or a family history of PD, and people who drink less caffeine than average.<sup>8, 37, 38</sup>

### Future Directions

Larger GWAS studies are now being done to more clearly define the genomic signature of DLB risk, and whole genome sequencing efforts (which are needed to identify rarer genetic risk factors) are in the planning stages. Understanding how lifestyle and environmental risk factors (e.g., diet, pollutants) affect risk of dementia, in general, and DLB, in particular, currently lags behind genetics. This is due, in part, to the difficulties in studying the exposures that may take place years prior to the onset of symptoms. Studies of environmental factors should include the microbiome; for example, links have been found between certain oral bacteria and increased or decreased risk of AD. Almost completely unexplored at this point with respect to DLB is the field of epigenetics, or how the environment interacts with the genome to alter disease susceptibility and responsiveness to specific medications. ■

# Clinical Trials

Interested readers may consult the federally funded [ClinicalTrials.gov](https://www.clinicaltrials.gov) database for descriptions of all ongoing and completed clinical trials in DLB, as well as results of completed trials.

A few clinical trials have been done to test the effectiveness of drugs originally developed for AD (acetylcholinesterase inhibitors and the glutamate receptor blocker memantine) in people with DLB. Only one randomized, double-blind, placebo-controlled clinical trial of a drug for DLB has been conducted to date — of the acetylcholinesterase inhibitor donepezil. Donepezil proved effective in improving cognitive function in DLB patients,<sup>39</sup> and was approved in Japan for use in DLB as of 2014. (Visit [lbda.org/donepezilapproval](https://www.lbda.org/donepezilapproval) for more information on this study.) As of this writing, donepezil is the first drug ever to be approved by a regulatory agency specifically for the treatment of DLB.

(Rivastigmine, which is in the same class of drugs as donepezil, was previously approved by the FDA for treatment of dementia in Parkinson's disease.)

Studies are being developed now to test two novel drugs for use in DLB. The compound RVT-101, which acts on serotonin receptors to increase release of the neurotransmitter acetylcholine, will be tested for its ability to improve cognitive symptoms in the HEADWAY-DLB trial. Nelotanserin, another drug that acts on serotonin receptors, will be tested for its ability to alleviate visual hallucinations and RBD.

## Future Directions

Key areas for the development of new treatments for DLB include the following.

**Novel treatment approaches.** A trial is currently underway to test deep brain stimulation (DBS) in DLB. In DBS, an electrode is implanted in the patient's brain to stimulate a malfunctioning neural circuit. This technology, which is similar to that used in cardiac pacemakers, has been approved in the U.S. for use in treating certain motor disorders (PD, essential tremor, and dystonia), and has shown promise in treating depression, obsessive-compulsive disorder, and epilepsy.

**Targeting early stages of DLB.** Treatments are more likely to be effective in slowing the progress of a disease if initiated at the first signs of it. Another key area for future research in this area is to develop and test drugs to treat the MCI stage of DLB. (Before that can be done, however, researchers must develop standard diagnostic criteria for MCI-DLB.)

**Drugs for PDD and PD-MCI.** Drugs that are effective in treating cognitive symptoms of PDD and/or PD-MCI may well prove useful in DLB too. The cholinesterase inhibitor, rivastigmine, has been shown to be effective in both PD and PD-MCI. The serotonin receptor antagonist SYN120 is currently in clinical trials for treatment of PDD. Safinamide and rasagiline, two drugs that block the breakdown of dopamine, are in trials for treating PD-MCI, as is atomoxetine, a drug currently used to treat attention deficit disorder.

**Disease-modifying drugs.** The ideal drug for DLB would target the primary biological culprit in the disease: misfolded alpha-synuclein. A number of alpha-synuclein-targeting drugs, including both immunotherapies and small molecules, are currently under development. As mentioned above, many people with DLB or at risk of developing DLB could also likely benefit from drugs that prevent the development of amyloid plaques and tau tangles, and many drugs targeting those processes are now in development. Anti-inflammatory agents might also be added to treatment regimens to help prevent the harmful consequences of alpha-synuclein-provoked neuroinflammation. Another potential mechanism for drug development is enhancing the brain's ability to clear or degrade abnormally folded-proteins, such as alpha-synuclein. Better understanding of the genetics and biology of DLB will doubtless reveal other potential treatment targets.

**Non-pharmacological treatments.** Another avenue of study needed is treatments that do not include medications. It is not yet known what symptomatic benefits may be obtained from treatments such as exercise or cognitive behavioral therapy, or what nonpharmacological approaches to hallucinations may be most beneficial. Research into the benefits of caregiver education, training and support is also urgently needed.

**Development of better clinical trial enrollment criteria and outcome measures.** Clinical trials in DLB remain hindered by lack of easily measured clinical measures for identifying patients who might most benefit from drug treatments, and assessing drug effectiveness (efficacy). For example, identifying DLB patients with secondary AD

neuropathology is important for clinical trials for both AD and DLB. The development of accurate biomarkers for DLB is critical in this regard, as is the development of fast, cost-efficient tests (especially automated and/or Web-based ones) to monitor early cognitive and physiological changes. A recent trend in clinical trials is the use of patient-centered outcome measures in addition to objective data gathered based on clinical tests. Patient-centered outcome measures are data provided by patients and caregivers about how much and under what circumstances treatments are affecting their quality of life and their own perceptions of the severity of their symptoms. Patient-centered outcome measures are now being adopted in the the AD field, but have not been used yet in DLB trials.

**Recruiting patient cohorts.** The recruitment of large patient cohorts is essential to carrying out well-designed clinical trials, as well as for longitudinal studies aimed at identifying accurate biomarkers and robust outcome measures for clinical trials.■

# The LBD Community: Partners in Research

In the past, disease research has been the largely exclusive domain of academic researchers and drug companies, who have often worked in isolation from one another and from the patient and caregiver community. Today, a new model for disease research is evolving. This model involves open, coordinated collaborations between academic researchers, pharmaceutical and biotech companies, private foundations and government agencies.

Importantly, it also includes patients, caregivers and patient advocacy groups as key collaborators, knowledge resources and decision-makers. A team approach will be particularly critical for speeding progress in DLB because of the complex biology and varying symptoms of the condition and the difficulty in recruiting sufficiently large patient cohorts for clinical trials.■

A new model for disease research includes patients, caregivers and patient advocacy groups as key collaborators, knowledge resources and decision-makers.



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# Acknowledgments and References

## Acknowledgments

Science writing was provided by Gabrielle LeBlanc. Scientific review and editing assistance was provided by the following members of LBDA's Scientific Advisory Council: Bradley Boeve, MD; Dennis Dickson, MD; Douglas Galasko, MD; James Galvin, MD; Jennifer Goldman, MD; David Irwin, MD; James Leverenz, MD; Carol Lippa, MD; Oscar Lopez, MD; Ian McKeith, MD; Andrew Siderowf, MD; Andrew Singleton, MD; Daniel Weintraub, MD. This paper was supported by an unrestricted educational grant from Axovant Sciences.

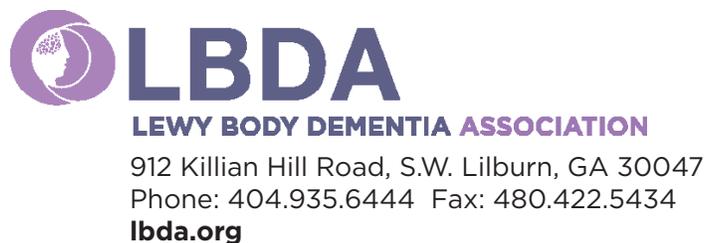
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*This publication is sponsored by an  
unrestricted educational grant from*



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