Published in final edited form as:

Neurol Clin. 2017 May ; 35(2): 325–338. doi:10.1016/j.ncl.2017.01.004.

Lewy Body Disorders

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Keywords

Lewy body; α -synuclein; Dementia; Diagnosis; Management

INTRODUCTION

Dementia syndromes associated with Lewy body pathology are subdivided into dementia with Lewy bodies (DLB) and Parkinson disease with dementia (PDD), arbitrarily based on the timing of cognitive decline in relation to motor symptoms. DLB is an underdiagnosed cause of dementia in the elderly. In addition to symptoms of Alzheimer disease (AD) and Parkinson disease (PD), DLB has distinctive neurobehavioral and cognitive features.^{1,2} A major clinical diagnostic question is how to distinguish DLB and AD. PDD starts with the movement disorder characteristic of PD, followed by cognitive decline after years or even decades. PDD, therefore, is not a diagnostic puzzle. The distribution of pathology in DLB and PDD helps to explain the diversity of symptoms.^{3,4} The key pathologic feature in these disorders is aggregation of the protein α -synuclein, forming structures called Lewy bodies (LB) in neuronal cell bodies and neurites in neuronal processes. Much evidence implicates the spread of α -synuclein between neurons in the progression of disease.

THE WHAT AND WHERE OF DEMENTIA WITH LEWY BODIES PATHOLOGY

In addition to the classic involvement of the substantia nigra in PD, α -synuclein pathology has a predilection for the olfactory nerve, branches and nuclei of the vagus nerve, and the locus ceruleus and other brainstem nuclei.⁵ Dysfunction of these structures results in loss of sense of smell, constipation and autonomic dysfunction, altered alertness, and rapid eye movement (REM) sleep behavior disorder (RBD), which are common to both PD and DLB and may precede motor or cognitive symptoms by years.⁶ In DLB and PDD, α -synuclein pathology includes cortical regions of the brain.

In DLB, there are 3 variations of α -synuclein pathology: brainstem predominant, limbic (also called transitional), and neocortical. Brainstem lesions affect the substantia nigra, nuclei of the vagus and glossopharyngeal nerves, reticular nuclei, and locus ceruleus. Limbic or transitional pathology occurs in the amygdala, transentorhinal cortex, and cingulate. Neocortical pathology is found in areas such as the temporal, frontal, and parietal cortex. Limbic and neocortical α -synuclein lesions are associated with clinical features characteristic of DLB and also distinguish PDD from PD.⁴ AD pathology often coexists in DLB and PDD. Concomitant AD pathology contributes to cognitive impairment and may

mask or attenuate the neurobehavioral features of DLB. Unlike AD pathology, LB and Lewy neurites in the neocortex are not obviously associated with neuron loss or atrophy.

Is the association of AD and α -synuclein lesions a coincidence? In sporadic DLB and PDD, AD pathology may also be present simply because of age. However, about 20% to 30% of patients with autosomal dominant early onset familial AD have widespread α -synuclein pathology,⁷ and a similar proportion of people with Down syndrome (DS), who develop accelerated AD pathology, also have α -synuclein lesions. This finding suggests more than a chance relationship because the onset of dementia in familial AD and DS is younger than the typical age of onset of PD. How amyloid pathology may accelerate α -synuclein aggregation in a subset of people is unknown.

EPIDEMIOLOGY AND RISK FACTORS

Autopsy studies from research centers suggest that DLB pathology occurs in about 20% to 25% of cases of dementia in the elderly. However, more thorough studies using antibodies against α -synuclein reveal amygdala pathology in as many as 40% to 50% of cases. The clinical significance of amygdala-only α -synuclein pathology is unclear, as no unique or characteristic features identify these patients during life. In brains originating from community-based studies, the frequency of DLB pathology is lower, about 10%.⁸ The prevalence of DLB has rarely been assessed in population-based clinical studies. It is estimated to account for about 4% of cases of dementia in community-based studies and about 7% in clinic series.⁹ Clinical and pathologic studies indicate that age is a risk factor for DLB: the typical age at onset ranges from about 70 years to 85 years. DLB is more common in men than women, as is RBD, one of the characteristic symptoms associated with brainstem LB. DLB has been studied mainly among Caucasian and Japanese populations, and its worldwide occurrence is unknown. Although there are no environmental factors that have been definitively shown to modify the risk of DLB or PDD, one study has suggested that caffeine intake may be a protective factor.¹⁰

Cognitive impairment is common in PD, and dementia may eventually affect as many as 80% of patients.^{11,12} Age and PD duration are the leading risk factors for PDD. The underpinnings of PDD include degeneration of nuclei and pathways involving cholinergic, dopaminergic and noradrenergic pathways,¹³ α -synuclein pathology in the medial temporal lobe, and coexisting AD pathology in more than 50% of cases.¹⁴

Many genetic alterations contribute to PD. The most common of these are leucine rich receptor kinase 2 (*LRRK2*) mutations (particularly G2019S, which is found worldwide, with an increased frequency in people of Ashkenazi Jewish or North African descent) and glucocerebrosidase A (*GBA*) mutations. Mutations in the gene for α -synuclein (*SNCA*) are rare. People with PD due to *GBA* and *SNCA* mutations have a high likelihood of developing cognitive decline and a clinical picture of DLB. Genome-wide association studies for late-life DLB or PDD have identified 5 genes linked to PD that are also associated with the risk for DLB and/or PDD, namely, *GBA*, *LRRK2*, microtubule-associated protein tau (*MAPT*), scavenger receptor class B member 2 (*SCARB2*) and *SNCA*.¹⁵ Also, apolipoprotein E (*APOE*) e4, the strongest genetic risk factor for late-onset AD, is linked to DLB and PDD.¹⁶

Shared PD and AD genetic risk is consistent with the admixture of α -synuclein and AD pathology in DLB. Although genetic factors may shed light on mechanisms of disease, there is no role for clinical genetic testing in DLB or PDD at present.

DIAGNOSTIC CRITERIA AND A CLINICAL APPROACH TO PARKINSON DISEASE WITH DEMENTIA AND DEMENTIA WITH LEWY BODIES

Diagnostic criteria for PDD¹⁷ focus on the assessment of cognitive decline and its impact on functional abilities. At the stage of PD when dementia typically occurs, neuropsychiatric, sleep, movement, and autonomic symptoms may be present. The difficult part of the diagnosis is determining whether functional impairment results from cognitive changes and is not solely due to advanced motor features of PD. By contrast, the major clinical problem in DLB is distinguishing it from AD. Diagnostic clinical criteria for DLB were developed in 1996¹ and updated in 2005.² The 1-year rule was proposed to split DLB and PDD: PDD is diagnosed if motor symptoms precede cognitive decline by more than a year; DLB is used if cognitive decline precedes or accompanies the first motor symptoms. These distinctions are arbitrary, and it may sometimes be difficult to judge which symptom started first. Separating DLB and PDD has been questioned because the clinical features and brain pathology overlap. However, for research purposes and to enhance diagnostic awareness, DLB remains a useful concept. Table 1 lists the clinical features and Table 2 the biomarkers that may be used to evaluate patients with PDD and DLB. The discussion that follows focuses on DLB, but the approach to PDD is similar.

CORE CLINICAL FEATURES

The essential feature of DLB is the *D* (dementia), referring to cognitive decline sufficient to interfere with independence in complex daily activities. This cognitive decline typically has a gradual onset. Progression is similar to that of AD, although sometimes DLB may progress more rapidly. The pattern of cognitive impairment in DLB may differ from AD, with selective deficits on tests of attention, visuospatial, and executive function.¹⁸ Symptoms related to visuospatial difficulty include sitting down on the edges of chairs, tripping on stairs, or misjudging distances while driving. General cognitive symptoms in DLB include forgetfulness; impaired judgment, organization, and planning; and getting lost. Memory impairment may not be prominent early in DLB, although patients with significant concomitant AD pathology show deficits on tests of memory and learning. Brief screening tests, such as the Mini-Mental State Examination (MMSE), may be insensitive to the early cognitive changes of DLB or PDD. Formal neuropsychologic testing can more clearly identify deficits characteristic of DLB.

The clinical features of fluctuation, hallucinations, and parkinsonism are called core features of DLB.¹ The original diagnostic criteria for DLB specified that dementia plus 2 or more core features (fluctuation, hallucinations, parkinsonism) defined probable DLB. One core feature indicated possible DLB, whereby there is a lower likelihood that α -synuclein pathology contributes to dementia. These criteria are currently under revision and will elevate RBD to a core feature and include the use of biomarkers to support a diagnosis of probable DLB.

Fluctuation refers to changes in alertness, attention, and cognition and includes periods of decreased attention, staring spells, or confusion, lasting from seconds to hours. Although it is sometimes striking, fluctuation may be difficult to identify in DLB. Research tools to assess fluctuation include a detailed informant-based diary or the use of psychometric tests that measure variability in choice reaction time. A brief questionnaire about fluctuation¹⁹ and a set of 4 questions about daytime drowsiness, sleeping 2 hours or more per day, staring into space, or episodes of disorganized speech²⁰ are more practical. In patients with varying alertness, delirium may need to be considered; the workup should include factors such as infection, dehydration, uncontrolled medical disorders, and the effects of central nervous system-active medications.

Hallucinations, most commonly visual, are characteristic of DLB. Patients typically report recurrent, complex visual hallucinations, for example, seeing people, animals, or insects, and may describe them in great detail.¹ Patients may misinterpret shadows or patterns as people or objects, referred to as illusions. Patients with DLB with visual hallucinations have more severe visuospatial dysfunction than those without.²¹ Patients may find the hallucinations frightening and can develop delusions related to them. In PD, hallucinations occur in about 30% of patients, persist even after doses of dopaminergic medications are decreased, and may be a predictor of dementia. The anatomic basis of hallucinations is not clear, although weakening of interactions between neural networks for attention and conscious perception may be important.²² The burden of LB in the inferior temporal lobe plus cholinergic deficits in the temporal lobe and other cortical areas may play a role. Visual hallucinations occurring only in a setting of delirium are not evidence for a diagnosis of DLB. In the presence of severe vision loss, recurrent and vivid visual hallucinations suggest Charles Bonnet syndrome rather than DLB.

In DLB, parkinsonian motor signs may be milder than those typically found in idiopathic PD.^{23,24} Rest tremor may be less common in DLB than in PD/PDD; axial signs, such as stooped posture, slowing of gait, and postural instability, may be more prominent. Tremor in DLB may worsen with walking or show overflow (involvement of a wider distribution of muscles) when standing.²⁵ Assessment of parkinsonism in patients with advanced dementia may be difficult because cognitive impairment and apraxia limit their ability to follow instructions to perform motor tasks. Assessment of gait and postural instability are an important part of the examination regardless of diagnostic specificity. Patients with DLB do not always show a good or prolonged response to L-dopa, but a trial of treatment is warranted.²⁶ This point may be explained by widespread pathology in DLB that directly affects the striatum and also by deficits in nondopamine neurotransmitter pathways. Other causes of slowing of gait and impaired balance in elderly people include vascular pathology affecting subcortical structures (eg, extensive white matter hyperintensities on MRI or lacunar infarcts) as well as arthritis, pain, deconditioning, and fear of falling. Parkinsonian findings may also be secondary to dopamine receptor blocking actions of potent neuroleptic drugs.

RBD occurs frequently in patients with α -synuclein pathology, including DLB, PD, and multisystem atrophy.²⁷ It may precede these diagnoses by years, consistent with the idea that α -synuclein pathology spreads or advances from the reticular activating system and nuclei

such as the locus ceruleus to the substantia nigra and later to limbic and cortical regions. RBD is much more common in men than women. Its symptoms are due to the lack of motor inhibition during REM sleep. During periods of REM sleep, patients make vocalizations and movements, such as shouting, grunting, thrashing, punching, or kicking, and seem to act out their dreams. They may describe frightening dreams if awakened, such as being chased. Symptoms of RBD can be disturbing to the patients' bed partner and can result in injuries if patients fall out of bed. The history alone may strongly indicate RBD. A formal sleep study may be needed to confirm RBD if there is serious sleep disruption. Other disturbances during sleep and arousal are common in DLB and PDD, including daytime drowsiness, obstructive sleep apnea, and periodic limb movements in sleep, and may warrant polysomnography.

SUGGESTIVE FEATURES FOR DEMENTIA WITH LEWY BODIES

Several clinical features in patients with DLB are either less specific or not common enough to be considered as core features. These features have been termed *suggestive* in consensus criteria for DLB and include neuroleptic sensitivity, autonomic symptoms, repeated falls, delusions, and depression. Neuroleptic sensitivity was first reported in elderly patients with DLB treated with typical antipsychotic medications but later in some patients treated with atypical agents.^{1,2} 'Sensitivity included marked cognitive and motor deterioration that could require hospitalization and was sometimes fatal. Therefore, use of neuroleptics in DLB is discouraged and a neuroleptic challenge should not be considered as a diagnostic test. Dysfunction of the autonomic nervous system is common in DLB, PD, and PDD and due to α -synuclein pathology in central autonomic pathways, such as branches of the vagal nerve or in neurons in paraspinal autonomic ganglia. The most prominent symptoms are orthostatic hypotension and syncope, whereas others may include erectile dysfunction, excess salivation, constipation, altered sweating, and seborrhea. Transient loss of consciousness or awareness may be due to presyncope or to fluctuation. Urine incontinence is common in dementia and aging from a variety of causes and is not a specific indicator of autonomic problems in DLB. Patients with DLB and PDD may have repeated falls because of parkinsonism, impaired postural reflexes, autonomic impairment and impaired visuospatial judgment, and also general factors, such as aging, deconditioning due to lack of activity, and dementia. Delusions are fairly common in DLB, as in other dementias. In some patients they may relate to the visual hallucinations and may be systematized. Depression is common in DLB. Apathy without a depressed mood may be prominent, although not specific. With the progression of dementia, anxiety and agitation often develop and may require treatment.

EARLY STAGES OF PARKINSON DISEASE WITH DEMENTIA AND DEMENTIA WITH LEWY BODIES

Disease-modifying treatment of PDD and DLB is more likely to succeed when started as early as possible; therefore, early diagnosis is a priority. For PD, a stage of mild cognitive impairment (MCI) was recently defined²⁸ and prodromal DLB is being studied.²⁹ Loss of sense of smell and constipation are overrepresented in patients with DLB and PD, and may

occur years before cognitive or motor symptoms. However, these symptoms are nonspecific. RBD is a strong predictor of PD or DLB.³⁰ The cognitive profile of MCI that progresses to PDD or DLB varies: in some patients, mild deficits on visuospatial and executive tests occur, but others show an amnesic picture. Fluctuations and hallucinations rarely precede the general picture of DLB.

BIOMARKERS

Neuroimaging markers can help in the diagnostic workup of DLB. For PDD, they have research utility, because dementia is a clinical diagnosis in the setting of an established diagnosis of PD. Although there is no way to image or biochemically detect aggregates of α -synuclein in the brain, imaging may provide indirect evidence of α -synuclein pathology. Dopamine nerve terminal density in the basal ganglia, reflecting projections from the substantia nigra, can be imaged using single-photon emission computed tomography (eg, DaTscan) or PET. Decreased binding has sensitivity of about 80% for DLB and high specificity to distinguish DLB from AD.^{31,32} Peripheral sympathetic cardiac denervation, imaged using metaiodobenzylguanidine scintigraphy, is highly sensitive and specific for DLB.^{33,34} Occipital lobe hypometabolism occurs on fluorodeoxyglucose (FDG) PET imaging in about 70% to 80% of patients with DLB but not in AD.³⁵ The pathologic basis of this finding is not clear. The cingulate island sign, an area of preserved normal uptake in the mid-cingulate or posterior cingulate, is another FDG PET feature that is characteristic of DLB.³⁶

MRI shows relative preservation of the hippocampus and medial temporal lobe in DLB compared with AD and cannot clearly distinguish DLB from other causes of dementia.³⁷ Longitudinal MRI studies show similar rates of atrophy in patients with AD and those with DLB with concomitant AD.³⁸ In PD-MCI and PDD, changes on MRI include cortical atrophy, often with preservation of medial temporal lobe structures, and changes in white matter tracts.³⁹ PET imaging methods that detect fibrillar amyloid beta protein allow AD plaque pathology to be diagnosed during life. In one of the larger studies to date that examined people with a spectrum of α -synuclein disorders, those with DLB had a higher amyloid burden than those with PDD, PD-MCI, PD, or age-comparable controls. In DLB but not the other groups, the extent of amyloid burden correlated with scores on tests of semantic memory but not other cognitive domains.⁴⁰ This finding suggests that fibrillar amyloid pathology may be more relevant to DLB than to PDD. PET imaging probes of abnormal fibrillar forms of tau were recently developed. In a preliminary study in PD/DLB/PDD, some patients showed increased tau uptake in areas, such as the inferior temporal gyrus, precuneus, and neocortex, which correlated with impaired cognition. This finding reaffirms that tau pathology may contribute to cognitive deficits across the PD/PDD/DLB spectrum.⁴¹

Analysis of electroencephalogram shows differences between DLB and AD, particularly in posterior regions (reviewed in Ref.⁴²), but measures and methods have not been validated for routine use. Cerebrospinal fluid (CSF) biomarkers can provide evidence of AD-related pathophysiology (low CSF A β 42 and high tau). Patients with DLB are more likely to have low CSF A β 42, sometimes with increased total tau or phospho-tau (P-tau) 181.⁴³ In a recent

multicenter study, about two-thirds of patients with DLB had decreased CSF A β 42 and almost one-third had increased tau or P-tau levels. Abnormally low A β 42 or increased tau or P-tau was associated with more rapid cognitive decline over 24 months.⁴⁴ In patients with PD, decreased CSF A β 42 is related to a higher risk of progressive cognitive decline,⁴⁵ consistent with amyloid PET studies indicating that coincidental AD amyloid pathology is associated with faster clinical progression. CSF levels of α -synuclein may be slightly decreased in DLB or PD relative to AD and controls, but these are not diagnostically useful.⁴⁵ Recently, it was found that oligomeric α -synuclein is increased in CSF in DLB and PDD⁴⁶; this promising initial finding requires validation.

MANAGEMENT AND TREATMENT OF PARKINSON DISEASE WITH DEMENTIA AND DEMENTIA WITH LEWY BODIES

Overall management begins with a detailed evaluation of cognitive, behavioral, sleep, movement, and autonomic symptoms. Education of the family and caregivers about PDD or DLB, and about general concerns for patients with dementia, such as managing finances and medications, home safety, caregiving needs, and the importance of cognitive and social stimulation and maintaining physical strength and walking skills, are important. Organizations such as the Lewy Body Disorders Association (www.lbda.org) and the Alzheimer's Association (www.alz.org) are excellent resources for information about DLB, PDD, and caregiving.

Medications should be selected according to target symptoms. The decision to use a medication depends on the severity of the symptoms; for example, mild, nonthreatening, visual hallucinations may not require treatment. Table 3 shows target symptoms and lists some suggested medications. Of note, high-level evidence to support treatment of the diverse symptoms associated with DLB or PDD does not exist because there have been few clinical trials in this area.⁴⁷ Some options can be extrapolated from clinical trials on patients with AD or PD. In general, symptomatic medications should be started at low doses and titrated in light of target symptoms and side effects. It is best to introduce one new medication at a time to be able to clearly interpret benefits and side effects. The diverse symptoms associated with DLB and PDD often require use of multiple medications, some of which may interact. For example, an acetylcholinesterase inhibitor (AChEI) for cognition, a selective serotonin reuptake inhibitor (SSRI) for depression or apathy, an appropriate dose of L-dopa for parkinsonism, and an atypical antipsychotic to control hallucinations may all be needed. To limit the potential for drug-drug interactions, medications that do not clearly help after a reasonable trial should be stopped.

For parkinsonism in DLB, a trial of L-dopa is recommended. Because L-dopa may worsen neurobehavioral symptoms, a low dose should be started and increased slowly. The clinical response to L-dopa may be less dramatic in DLB than in idiopathic PD,²⁶ although some patients show improvement in gait, movement speed, and even alertness. Dopamine agonists are problematic in DLB because of their high risk of provoking behavioral symptoms or other side effects. In PDD, similar careful titration of L-dopa and other medications is needed to obtain the best balance between benefits and side effects.

For cognitive impairment, a trial of an AChEI, such as donepezil, rivastigmine, or galantamine, is worthwhile. Neuropathologic studies report a severe cholinergic deficit in limbic and cortical regions in DLB, suggesting that these patients may be particularly responsive to AChEI treatment. Randomized clinical trials of AChEIs have been conducted in DLB^{48,49} and PDD.⁵⁰ The first trial in DLB assessed rivastigmine and found no major effect on the MMSE but significant improvement on computerized tests of attention and a trend for benefit on behavioral symptoms. A later trial of donepezil found benefits relative to placebo on the MMSE that were maintained with open-label follow-up for 52 weeks.⁴⁹ A trial of rivastigmine in PDD showed favorable treatment-placebo differences in measures of cognition (including computerized timed tests of attention), global ratings, and activities of daily living. Rivastigmine did not affect parkinsonism, although 10% of patients showed worsening of tremor.⁴⁷ Gastrointestinal side effects were the most common reason to discontinue AChEIs in all of these trials. Although evidence is limited,⁴⁷ it is reasonable to try an AChEI for cognition or fluctuation in DLB or PDD. Memantine is approved for the treatment of AD. In DLB and PDD, randomized clinical trials found that memantine was safe and well tolerated and had small effects on global ratings and tests of attention but not on other cognitive or behavioral symptoms.^{51,52}

Apathy and decreased initiative may contribute to cognitive and functional impairment and are not necessarily part of depression. Although L-dopa may incidentally help these symptoms, other medications may be worth considering if apathy and inertia are disabling. SSRI or serotonin-norepinephrine reuptake inhibitor antidepressants may be tried, with experience drawn from their extensive use in depression in PD.⁵³ Sometimes apathy is accompanied by daytime hypersomnia. Additional treatment possibilities in this situation may include stimulants, such as methylphenidate or modafinil. Anxiety and depression may co-occur in PDD and DLB. Although evidence from formal clinical trials is limited, analyses suggest that SSRIs are better tolerated and may be more efficacious than tricyclic antidepressants in PD.⁵⁴

For behavioral symptoms, such as hallucinations, psychosis, and agitation, non-medication approaches, for example, distraction, should be tried. For delusions and agitation, the impact of general health factors (eg, pain, infections) and environmental and interpersonal triggers should be explored. If high doses of L-dopa are being used, reduction may lead to improvement. Visual hallucinations may require drug treatment only if they are disturbing to patients. Sometimes AChEI treatment may help with hallucinations.⁴⁸ Typical neuroleptics should be avoided because of risks of worsening parkinsonism or causing severe reactions with cognitive and motor decline (neuroleptic sensitivity). Atypical antipsychotic agents, such as olanzapine or risperidone, should be used cautiously because they have weak D-2 receptor blocking activity. Atypical antipsychotic agents, such as quetiapine or clozapine, have support from clinical trials in PD with psychotic symptoms (reviewed in Refs.^{47,53}), although the blood monitoring required for clozapine makes it impractical. Many classes of medications have been tried for delusions and agitation in patients with dementia but lack evidence from randomized clinical trials. Medications, such as trazodone, and anticonvulsants, such as valproate, gabapentin, or topiramate, may be considered. Sedatives, such as alprazolam, should be avoided because of risks of confusion and falls. Meta-analyses of elderly patients treated with neuroleptic medications have shown increases in morbidity

and mortality,⁵⁵ and these medications carry a black box warning from the Food and Drug Administration (FDA). Nevertheless, the judicious use of atypical antipsychotic agents, such as quetiapine (which has an advantage of being short acting), can be considered, at least as a short-term intervention, with careful clinical monitoring for potential side effects, such as drowsiness. Pimavanserin, a serotonin inverse agonist, recently received FDA approval for treatment of hallucinations and delusions associated with PD psychosis⁵⁶ based on 6 weeks of treatment in a randomized clinical trial. Postmarketing data will be important to determine its longer-term benefits and safety.

Sleep disorders in patients with DLB/PDD should be carefully characterized to determine the best treatment. If the clinical description is inadequate or uncertain, polysomnography is helpful. For obstructive sleep apnea, standard approaches, such as nasal continuous positive airway pressure or bi-positive airway pressure, may improve symptoms. To control RBD symptoms, melatonin or clonazepam are worth- while.²⁷ For insomnia, similar medications to those used for agitation may be considered as well as low doses of benzodiazepines, such as zolpidem. Newer sleep- promoting agents, such as eszopiclone, zaleplon, and extended-release zolpidem, have a theoretic advantage of lower risk of tolerance but have not been formally studied in patients with DLB.

FUTURE DIRECTIONS

Revised diagnostic criteria and use of biomarkers may help to develop earlier and more accurate diagnosis of DLB and stronger predictors of PDD. Further studies will clarify whether there are biological and meaningful clinical differences between DLB and PDD. Genetic studies may improve our understanding of mechanisms of disease and suggest new treatment targets. Biomarkers that allow monitoring of α -synuclein pathology would greatly help with disease staging and development of disease-modifying treatment. Because the pathology of many patients with DLB includes deposition of amyloid beta protein, it is likely that anti-amyloid treatments will be useful in DLB and in some patients with PDD.

Acknowledgments

Dr D. Galasko has received research funding from the National Institute on Aging, the California Institute for Regenerative Medicine, the Alzheimer's Drug Discovery Foundation, and from the Michael J. Fox Foundation. He has received honoraria for serving as an advisor to vTv Therapeutics. He is a paid editor for the journal *Alzheimer's Research and Therapy*. He has served on data safety boards for Eli Lilly and Company and Prothena Inc.

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KEY POINTS

- Cognitive disorders associated with Lewy Bodies are arbitrarily divided into Parkinson's Disease-Dementia and Dementia with Lewy bodies depending on the order in which symptoms arise.
- Clinical evaluation should include movement, cognition, behavior, sleep and autonomic function.
- Biomarkers including brain imaging and polysomnography may be helpful diagnostic tools.
- Medications can help to manage many of the diverse symptoms.

Table 1

Clinical and diagnostic features of dementia with Lewy bodies and Parkinson disease with dementia

	DLB	PDD
Major clinical features		
Chronology of symptoms	Dementia precedes or occurs together with onset of motor features of parkinsonism.	Motor symptoms precede dementia by 12 mo or longer, often by many years.
Dementia	It may have prominent deficits on tests of attention, executive function, and visuospatial ability. Memory impairment is often less prominent at onset but occurs with progression and if there is concomitant AD.	It is similar to DLB.
Fluctuating cognition	There is marked variation in alertness and attention.	It may be present.
Hallucinations	It is recurrent, most often visual, well formed (eg, people, animals), and detailed.	It is often present.
Motor parkinsonism	It is variable, may be mild; tremor is often absent.	It is more likely to be moderate to severe when dementia develops.
RBD	RBD is more common in men. It may precede DLB or PDD.	
Associated clinical features	Features include daytime sleepiness, transient episodes of unresponsiveness, neuroleptic sensitivity, orthostatic hypotension, urine incontinence, constipation, falls, and anosmia.	

Clinical features grouped as associated have been called supportive or suggestive in consensus criteria for DLB and also occur commonly in PDD but are not essential for diagnosis.

Adapted from Refs. 2,15,57

Table 2

Neuroimaging and other biomarkers in the diagnosis of Lewy body dementia

Biomarker	DLB	PDD
Dopamine transporter imaging using SPECT or PET	Low dopamine transporter uptake in basal ganglia	Not needed for diagnosis unless PD has not been previously diagnosed
MIBG cardiac scintigraphy	Decreased uptake	
Polysomnography	Confirms RBD Can identify other sleep problems, for example, obstructive sleep apnea, periodic movements of sleep	
MRI structural imaging	MRI structural imaging Relative preservation of medial temporal lobe structures, unless AD is also present	
EEG	Prominent posterior slowwave activity on EEG with periodic fluctuations in the prealpha/theta range	—
CSF A β 42, tau, P-tau 181	Concomitant AD pathology indicated by decreased CSF A β 42 and increased tau or P-tau 181 CSF a-synuclein Decreased levels of a-synuclein in CSF	
CSF α -synuclein	Decreased levels of α -synuclein in CSF in DLB or PDD not diagnostically helpful because of extensive overlap with controls and with AD	

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram; MIBG, metaiodobenzylguanidine; SPECT, single-photon emission computed tomography.

Table 3

Medications to treat symptoms of Lewy body dementia (Parkinson disease with dementia and dementia with Lewy bodies)

Symptoms	Medications	Comments
Cognitive impairment		
Forgetfulness, poor attention, fluctuation	AChEIs: Donepezil Rivastigmine Galantamine Memantine	Tolerability of AChEIs possibly limited by gastrointestinal side effects Minimize concomitant medications with anticholinergic effects Well tolerated, but small effect
Apathy, decreased initiative, psychomotor slowing	Antidepressants, for example, SSRI or SNRI drugs Stimulants, for example, modafinil	Sometimes improves on L-dopa and/or AChEIs Possible side effects, such as orthostasis, with older antidepressants, for example, tricyclic antidepressants
Motor impairment		
Bradykinesia, slowing of gait, increased tone, tremor	L-dopa/carbidopa Dopamine agonists, for example, ropinirole	Hallucinations, anxiety, agitation, sleepiness Higher risk of hallucinations in DLB and PDD
Neuropsychiatric symptoms		
Hallucinations, delusions	AChEIs Clozapine Risperidone, olanzapine, aripiprazole Quetiapine Pimavanserin	Small effects on these symptoms Needs regular monitoring of blood count Black box warning, risk of neuroleptic sensitivity Black box warning Short acting, wide dose range Effective in 6-wk RCT; lacks postmarketing safety data
Agitation, insomnia	Atypical antipsychotics Trazodone, gabapentin, topiramate, valproic acid	Black box risks No evidence from RCTs, but widely used, for example, in AD
Depression	Fluoxetine, paroxetine, sertraline, citalopram	Tolerance of SSRIs potentially better than TCAs in PD
Anxiety	Paroxetine, sertraline, buspirone	Minimal study in RCTs in PD Benzodiazepines not recommended because of potential for confusion and falls
RBD	Melatonin Clonazepam	—
Daytime hypersomnolence	Stimulants, for example, modafinil	—
Autonomic impairment		
Orthostasis	Fludrocortisone Midodrine	Fluid retention, edema

Abbreviations: AChEIs, acetylcholinesterase inhibitors; RCT, randomized clinical trial; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.