Diagnosing and Managing
Lewy Body Dementia

A Comprehensive Guide for Healthcare Professionals

Provided by: LBDA
LEWY BODY DEMENTIA ASSOCIATION

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Did you know?

Lewy body dementia (LBD) affects an estimated

1.4 million Americans

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LBD is often misdiagnosed as a

mental disorder

or an other form of

dementia.

1. About Lewy Body Dementia

1.1 The LBD Spectrum

Lewy body dementia (LBD) is a brain disease characterized by a spectrum of symptoms involving disturbances of movement, cognition, behavior, sleep and autonomic function. Two related clinical disorders make up the LBD spectrum: **dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD).**

Individuals with DLB present with dementia as the early disabling symptom, plus other LBD symptoms, one of which may be parkinsonism. Others will present with motor symptoms resulting in a diagnosis of Parkinson's disease (PD) and may also have some mild cognitive impairment initially or in the early stages of the disease; over time, usually several years or more, some will progress to dementia (PDD).

1.1.1 Dementia with Lewy Bodies

DLB is the second most common form of degenerative dementia in the elderly next to Alzheimer's disease (AD). Recent estimates suggest that DLB represents 4 to 16% of cases of dementia seen in the clinic,[1] but the true prevalence is probably higher.[2] The most common features of DLB are progressive cognitive impairment leading eventually to full-blown dementia, parkinsonian motor symptoms (tremor, slowed mobility, stiffness of muscles, stooped posture, shuffling gait), visual hallucinations, and fluctuations in levels of alertness and cognitive acuity. Other symptoms include acting out dreams (REM sleep behavior disorder) and disturbances of autonomic function (low blood pressure, constipation and urinary frequency).[3] Severe sensitivity or over-reaction to antipsychotic drugs (aka neuroleptics) are also common.

DLB is often misdiagnosed as AD, especially in those individuals who have few, if any signs of motor parkinsonism.[4] Diagnosis is challenging because the order of symptom appearance, their relative severity and the combination of features present varies among individuals.

1.1.2 Parkinson's Disease Dementia

PD is a common movement disorder that affects 1 in 100 individuals over the age of 60 and 4-5% of adults over age 85 (up to 1 million Americans).[5,6]

Original descriptions of PD in the medical literature did not recognize cognitive problems as an important clinical feature. More recently, clinicians have come to realize that PDD occurs often and is among the most debilitating symptoms associated with disease progression.

Each year an estimated 14% of PD patients over age 65 will develop at least mild dementia. In one study, almost 80% of PD patients developed dementia over an 8-year period.[7,8]

1.2 Cause and Pathology

The cause of LBD is unknown. Brain pathological changes in LBD involve selective damage and loss of nerve cells in certain regions of the brain (example: substantia nigra in the brainstem). Affected, but less damaged cells contain Lewy bodies, which are a microscopic aggregation of a specific protein (α-synuclein). The Lewy body is the pathological signature of LBD that overwhelms the cell's normal biological functions and causes it to die.[9] There are many possible causes of LBD but researchers are just beginning to understand the reasons why some people are more susceptible to developing LBD. One important reason that has recently come to light is the discovery of an increasing number of genetic variants that increase the likelihood that a person will develop LBD.

DLB and PDD are clinically similar, except for the timing of onset of cognitive impairment, but the pathology of the two is almost identical. This is both a surprise and a mystery, since there is no good explanation for the variability of the motor-cognitive interval among people with LBD. In other words, why do some people develop serious cognitive impairment at the earliest stage of a Lewy body disorder, whereas others remain cognitively normal for many years before impairment develops or never develop dementia?

Another puzzling fact is the frequent coexistence of the pathology of AD (amyloid plaques and neurofibrillary tangles) in DLB compared with PDD. AD differs from LBD clinically because of its distinctive cognitive profile (mostly a disorder of memory without the other features typical of LBD) and its lack of parkinsonian features except in late stages. The clinical overlap between AD and DLB in the absence of a specific diagnostic test leads to misdiagnosis in a significant minority of patients. Currently, the only way to definitively diagnose LBD is with an autopsy. These facts underscore the current concept of a neurodegenerative continuum with boundaries that are frequently blurred. It is only through research that these and other fundamental questions will be answered.

1.3 Risk Factors

Older age is the greatest risk factor for LBD, with most diagnoses being made in individuals over the age of 50. There is some evidence that the age of onset of the symptoms of DLB is younger than in PDD and the rate of progression/duration of disease is slightly faster in DLB.[10]

Rapid eye movement (REM) sleep behavior disorder (RBD), a condition characterized by dream enactment, is a common risk factor for DLB, PD and other synucleinopathies, often occurring many years before the onset of parkinsonism or cognitive impairment.[11] Pre-Parkinson's RBD is thought to increase the risk of cognitive impairment when the motor phase of PD evolves, compared with PD that has no RBD prodrome.

Parkinson's disease is a risk factor for developing dementia, since the majority of those with PD will eventually suffer from cognitive impairment.

1.4 Genetics

Mutations in over a dozen genes have been shown to "cause" PD.[12,13] Individuals with such rare genetic variants have a very high risk of developing PD during their lifetime, and many of them will later develop dementia. Mutations in one of these genes (*SNCA*) can occasionally result in a clinical picture that resembles DLB.[14] However, no more than 2% of patients with PD, and likely even fewer with DLB, carry a disease-causing mutation in a known gene. In most instances PD and DLB are thought to arise through a complex interaction between common genetic and environmental factors, each one with a small-to-modest effect. Two important common genetic risk factors that have recently come to light are variants in the *APOE* and GBA genes. The *APOE* ε4 allele has long been known to increase the risk of developing AD, but there is now strong evidence that it does the same for DLB.[15,16] Furthermore, patients with PD who carry *APOE* ε4 have (on average) more severe cognitive problems.[17] A number of variants in the *GBA* gene have been shown to increase risk for both PD and DLB.[18–20] In addition, patients with PD who have one of these *GBA* variants have a more rapid cognitive decline and are more likely to develop dementia.[21,22]

Since mutations that cause LBD are rare, and no treatments have been discovered to reverse the effects of known genetic risk factors, genetic testing is not currently recommended for routine screening.

However, if a family has multiple individuals with PD (with or without dementia) and/or DLB, it is reasonable to consider genetic testing for some or all of the known genes. The rationale for considering such testing would be to (1) confirm a diagnosis and (2) provide genetic counseling for family members, if the results are positive. These decisions need to be made carefully with family members and the individual's healthcare provider. It is prudent to undergo pre- and post-testing counseling so that the individual fully understands the risks and benefits of learning about their genetic status. In addition, certain research centers at academic institutions and the National Institutes of Health are investigating genetic risk and are actively seeking people who would like to volunteer as research subjects.

1.5 Research

In 2013, the National Institutes of Health organized a summit that resulted in the first national research strategy for LBD. Updated in 2016,[23] research priorities for LBD include:

- Developing new drugs for clinical trials.
- Establishing longitudinal studies culminating in autopsy studies to improve diagnosis of DLB.
- Determining which individuals with PD have a high risk of progressing to dementia.
- Developing a better understanding of the disease mechanisms through brain mapping and genetics.
- Identifying validated biological and imaging biomarkers to detect disease presence, measure progression and advance the development of safe and effective symptomatic and disease modifying therapies.

2. Symptoms of LBD

LBD has variable presentations that include cognitive difficulties associated with motor dysfunction, perceptual disturbances, and/or sleep/wake cycle alterations.

2.1 Cognitive

Cognitive impairment in DLB is often misdiagnosed as AD. While memory may be relatively intact in early DLB, the cognitive profile of DLB includes:

- Early and significant deficits in executive function, such as impaired planning, problem solving and judgment.
- Visuospatial dysfunction, resulting in difficulty recognizing familiar people or objects, problems with depth perception, or impaired hand-eye coordination.
- Reduced attention or ability to concentrate, which may mimic memory deficits.
- Slowed thinking (bradyphrenia) and speech difficulties may also occur.
- Fluctuating cognition is common and refers to changes in levels of attention, concentration and functional ability. Fluctuations may present as staring spells or confusion that lasts from minutes to hours. Transient episodes of unresponsiveness may also occur.

Mild cognitive impairment or unexplained delirium may be the earliest signs of impending LBD.

2.2 Motor

The onset timing of spontaneous parkinsonism in LBD varies and may be subtle at first. Signs and symptoms include:

- Reduced facial expression (masked facies)
- Soft voice (hypophonia)
- Stiffness (rigidity)
- Postural instability
- Gait difficulty and falls
- Slowness of movement (bradykinesia)
- Tremor at rest

2.3 Psychiatric

Recurrent visual hallucinations occur in up to 80% of people with LBD, and their appearance early in the course of dementia strongly suggests LBD[3]. People with LBD frequently report seeing people, animals or insects and can often describe them in great detail. Delusions are also common and may relate to visual hallucinations. Apathy, anxiety and depressive symptoms and signs are also frequently seen in LBD patients. Unfortunately, a severe sensitivity to antipsychotics is also a common symptom of LBD.

2.4 Sleep

REM sleep behavior disorder (RBD) may present years or even decades before other signs of LBD. RBD results from the absence of sleep paralysis that normally occurs during REM sleep, leading people to physically move about in their dreams. Patients may experience vivid nightmares and can shout, thrash, punch or kick during their dreams, sometimes injuring themselves or their bed partners. Idiopathic RBD is highly associated with the development of Lewy body disorders, both DLB and PD, but not AD.

Other sleep disorders include excessive daytime sleepiness, restless leg syndrome, insomnia, obstructive sleep apnea and periodic limb movement. A formal sleep study and treatment is recommended to resolve significant disruptions of sleep.

2.5 Autonomic

Severe autonomic dysfunction may occur in LBD, including orthostatic hypotension, syncope, erectile dysfunction, urinary incontinence and constipation. Other signs of autonomic dysfunction include excessive saliva and drooling (sialorrhea), altered sweating and a chronic, scaly skin condition (seborrhea). An impaired sense of smell (hyposmia) is also common, occurring earlier in LBD than in AD.

3. LBD Diagnosis

3.1 Neurological Exam

A thorough neurological examination should be conducted by a clinician experienced in neurodegenerative disorders at the time of the initial assessment. Areas of importance include:

- Cognitive function, including language and speech
- Eye movements (can be abnormal in some types of atypical parkinsonism)
- Gait, balance, fine/coarse motor movements, reflexes
- Presence of involuntary movements such as tremor
- Cortical sensory findings, such as assessing sensory abilities to recognize writing on the skin (graphesthesia) or objects by touch (stereognosis)
- Alteration of smell

Blood pressure should be taken at every visit to assess whether blood pressure drops significantly when a person moves from sitting or lying to standing (a measure of an impaired autonomic nervous system). As hallucinations are common, evaluation of vision and hearing can establish baseline acuity. Assessment of a person's functional status, including the ability to perform activities of daily living (bathing, dressing) and instrumental activities of daily living (managing money, shopping), can provide insight into the ability of patients to care for themselves.

Clinical follow-up should be done in 6 month intervals or whenever changes are reported by the patient or family.

3.2 Brief Cognitive Assessments

Select a brief standardized instrument sensitive for both amnestic and non-amnestic cognitive decline. The **Montreal Cognitive Assessment (MoCA)** has become the standard, whereas the **Folstein Mini-Mental State Exam (MMSE)** is also available, but is often not sensitive enough to detect initial, more-subtle cognitive deficits in LBD.[24] Each of these tests take less than 10 minutes to administer. Any ambiguous abnormalities will require referral for a more in-depth evaluation by a neuropsychologist.

For more information:

MoCA: http://www.mocatest.org/

MMSE: http://www.zielinskifam.com/papers/MMSE.pdf

3.3 Motor Assessment

Most people with DLB will experience parkinsonism over the course of the disorder, though it may be very subtle or not clinically apparent in the early stage. As such, it is not required for diagnosis. The **Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS)** is a helpful assessment tool for parkinsonism.

For more information:

MDS-UPDRS: http://www.movementdisorders.org/MDS-Files1/PDFs/Rating-Scales/MDS-UPDRS_English_FINAL.pdf

3.4 Psychiatric Assessment

Psychiatric symptoms are common and may include anxiety, depression and psychotic features such as hallucinations and delusions. If visual or other hallucinations occur with mild dementia, it is suggestive of DLB over AD. The most common tool used to assess psychiatric symptoms is the **Neuropsychiatric Inventory – Questionnaire (NPI-Q)**. This assessment gets information from a caregiver familiar with the patient's behavior and determines the frequency and the severity of each behavior.

For more information:

NPI-Q: https://www.alz.washington.edu/NONMEMBER/UDS/DOCS/VER2/IVPforms/B5.pdf

3.5 Sleep Assessment

REM sleep behavior disorder (dream enactment) frequently precedes the observed onset of LBD and the sleep partner should be asked about a history of acting out dreams. A **polysomnogram** is the gold standard in diagnosing RBD. The **SCOPA-SLEEP** assessment is a useful rating scale for night-time sleep and daytime sleepiness.

For more information:

SCOPA-S: https://www.lumc.nl/sub/7020/att/1288981/SCOPA-SLEEP-EN

3.6 Autonomic Assessment

There is not one standard test used to assess autonomic function in DLB, however, the **Non-Motor Symptoms Scale** or the **Scales for Outcomes in Parkinson's Disease (SCOPA)** assessments can be used.

For more information:

NMSS: http://www.movementdisorders.org/MDS-Files1/PDFs/MDS-UPDRS-Rating-Scales/NMSS30itemsrevised.pdf

3.7 Blood Tests and Imaging

Reversible causes of dementia (e.g. post-traumatic hydrocephalus, drug and alcohol toxicity, electrolytes, B12 deficiency, HIV, thyroid disorders), though rare in this setting, should be screened for and treated if confirmed.

Imaging by computed tomography (CT) or magnetic resonance (MRI) should be done to rule out stroke, brain tumors, intracranial bleeding, hydrocephalus or other structural causes of dementia. Imaging in DLB is usually normal. Dopamine transporter single-photon emission computed tomography (DaT SPECT) of the brain can be done when indicated to differentiate both DLB and PDD from AD. The scan in LBD usually shows reduced uptake of an injected radioactive compound that binds to the dopamine transporter compared with a normal result in AD.

Research is under way to identify neuro-imaging tests, as well as brain, spinal fluid and serum proteins (biomarkers) that can be used to help identify various types of dementia.

Did you know?

There are new

LBD clinical trials

and

longitudinal studies

that are now recruiting.

Go to

www.lbda.org/participate-in-research

3.8 DLB Diagnostic Criteria

In 2017, the international DLB Consortium published updated diagnostic criteria[3] (Table 1) for DLB in the journal *Neurology*.

Table 1: Revised Criteria for the Clinical Diagnosis of Probable and Possible DLB

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities.

- Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression.
- Deficits on tests of attention, executive function and visuoperceptual ability may be especially prominent and occur early.

Core clinical features

(NOTE: The first three typically occur early and may persist throughout the course.)

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

Indicative biomarkers

- Reduced dopamine transporter (DaT) uptake in basal ganglia demonstrated by SPECT or PET.
- Abnormal (low uptake) 123iodine-MIBG myocardial scintigraphy.
- Polysomnographic confirmation of REM sleep without atonia.

See open access article in Neurology3 for examples of abnormal scan results.

Supportive clinical features

Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction e.g. constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety and depression.

Supportive biomarkers

- Relative preservation of medial temporal lobe structures on CT/MRI scan.
- Generalized low uptake on SPECT/PET perfusion/ metabolism scan with reduced occipital activity +/- the cingulate island sign on FDG-PET imaging.
- Prominent posterior slow wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

Probable DLB can be diagnosed if:

a) two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or
b) only one core clinical feature is present, but with one or more indicative biomarkers

Probable DLB should not be diagnosed on the basis of biomarkers alone.

Possible DLB can be diagnosed if:

a) only one core clinical feature of DLB is present, with no indicative biomarker evidence, or
b) one or more indicative biomarkers is present but there are no core clinical features

DLB is less likely:

a) in the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation, or
b) if parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia.

DLB should be diagnosed when dementia occurs **before**, or **concurrently** with parkinsonism. The term Parkinson's disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson's disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD the existing one-year rule between the onset of dementia and parkinsonism continues to be recommended.

3.9 PDD Diagnostic Criteria

A consensus statement by a task force from the Movement Disorder Society for the diagnosis of PDD was published in 2007[25], providing criteria (Table 2) for probable and possible PDD.

A diagnosis of probable PDD requires the core features and a typical presentation of clinical features that is defined as having deficits in at least two out of four cognitive domains. There may or may not be behavioral symptoms, although their presence would support a diagnosis of probable PDD. There must not be any features present from Groups III and IV, as the abnormalities and conditions described in these categories can cause too much uncertainty in a potential diagnosis.

A diagnosis of possible PDD also requires the core features, but can have a more non-characteristic pattern of symptoms in at least one of the cognitive domains. There may or may not be any behavioral symptoms. One or more features of Group III may be present, and none in Group IV.

Table 2: Features of dementia associated with Parkinson's disease

Group I – The core feature requires a prior diagnosis of Parkinson's disease and dementia causing a decline in function severe enough to impair the patient in daily activities and in at least one cognitive domain.

Group II – The clinical features include both the cognitive and behavioral domains described below:
Cognitive domains:
- Attention – The patient shows a level of impairment in attention, which may fluctuate over time
- Executive function – Impairment in complex thought processes such as in initiating an action, planning, or organization
- Visuo-spatial ability – Marked deficits in the processing of visuo-spatial material
- Memory – There is noticeable impairment in both the recall of existing memories and in the learning of new material
- Language – Basic language features are largely intact, although there may be difficulties in finding words and understanding complex sentences

Behavioral domains:
- Apathy – Decreased spontaneity, motivation, effortful behavior
- Changes in personality and mood – Can include depression and anxiety
- Hallucinations – Usually complex and visual
- Delusions – Usually paranoid delusions, such as infidelity or perceived unknown guests in the home
- Excessive daytime sleepiness

Group III – The third category includes two features that will not rule out a diagnosis of PDD, but may make the diagnosis more uncertain:
- Existence of an abnormality such as vascular disease which causes cognitive impairment although not determined to cause dementia
- If the duration of time between the onset of motor and cognitive symptoms is not known

Group IV – The last domain contains two features which suggest that other existing conditions impair the patient's cognitive functioning to such an extent that reliable diagnosis of PDD becomes impossible.
1. Cognitive or behavioral symptoms which occur only in the context of existing conditions, such as systemic diseases, drug intoxication, or major depression
2. Symptoms compatible with vascular dementia, confirmed by an established relationship between brain imaging results and impairment in neurological testing

4. Discussing Diagnosis and Prognosis of LBD

4.1 Informing the Patient (and Caregiver)

The preparedness of patients and caregivers to receive an LBD diagnosis varies significantly between those with DLB and PDD. While there is increasing awareness of DLB among healthcare practitioners, public awareness remains relatively low. The multiple presenting features of DLB may raise suspicion in family members of more widely known disorders such as AD or PD, or alternatively, a possible psychiatric disorder. As most patients and families will first be introduced to DLB upon initially receiving the diagnosis, providing sound information and shaping appropriate expectations is essential to quality care. After a PD diagnosis, persons with PD and their caregivers are usually made aware of the potential of MCI or dementia to develop, so they may be more-well prepared to receive a PDD diagnosis.

While difficult news to receive, an LBD diagnosis can provide a certain degree of comfort as it helps patients and families make sense of their experiences. Discussion about LBD and its anticipated impact may take place over multiple office visits, due to the complexity of clinical and caregiving matters.

Documenting an LBD diagnosis is imperative, due to severe medication sensitivities and relatively low awareness of LBD outside of specialists. Family caregivers sometimes serve as the first line of defense against administration of traditional neuroleptics in hospitals. It is also critically important to make sure that one or more of the core manifestations of LBD is not caused or exacerbated by iatrogenic medications such as neuroleptics or anticholinergic agents.

4.2 Prognosis

Like AD, the rate of progression of LBD is highly variable. The typical lifespan after diagnosing LBD is about 5-7 years.[26,27] Anecdotal experience suggests that the trajectory of LBD progression may mirror the rate of early symptom onset and progression. The prospect of future therapeutic developments that may alter disease progression within this time frame should punctuate any discussion of prognosis.

4.3 Progression of LBD

There are no formally defined stages of LBD like there are in AD. Until then, expert insights may be useful to both the clinician and LBD family. Efforts are underway to define the mild cognitive impairment (MCI) stage of DLB to allow for an earlier diagnosis. Criteria have been developed for MCI in PD.[28]

4.3.1 Early, Suggestive Indicators of LBD

- Often recognized only in retrospect, possibly extending back 1-3 years.
- Occasional minor episodes of forgetfulness, sometimes described as lapses of concentration or 'switching off'.
- An initial brief period of delirium in association with genuine physical illness and/or surgical procedures, return to baseline, followed by a subsequent mental and physical decline.

4.3.2 Time for Diagnosis and Treatment

- Persistent cognitive impairment with marked fluctuations in severity.
- Nocturnal worsening and nightmares.
- More florid delirious episodes with confusion, visual and auditory hallucinations and secondary paranoid delusions.
- Occasional to frequent falls, either due to postural instability or sometimes accompanied by transient disturbances of consciousness.
- Extensive medical screening performed with negative results.

4.3.3 Advancing Disease

- Sudden increases in confusion, psychosis and behavioral disturbance may be precipitated by medication reactions or co-morbid medical conditions.
- Severe neuroleptic sensitivity reactions may provoke the rapid development of rigidity, marked worsening in cognitive functioning, and heavy sedation.
- In cases not receiving neuroleptics or tolerating low dosage of one, the typical natural history is a gradually progressive decline into severe dementia.
- Physical and speech therapy may help maintain functional abilities for some time.
- Increasing behavioral disturbances, including shouting, aggression on approach and evidence of persisting delirium.
- Death is usually due to respiratory or cardiac disease, or injuries sustained in falls.

Did you know?

More than

3/4

of persons with DLB are given a

different diagnosis initially.

Did you know?

People with LBD are often

more sensitive

to medications than individuals with

Alzheimer's disease.

• • •

Treatments

are available (off-label) to address many

LBD symptoms.

5. Treatment of LBD

The importance of early treatment is supported by recent data suggesting that patients with LBD, might respond better to cholinesterase inhibitors than patients with AD. In addition, an early diagnosis of DLB will help treating physicians know which medications to avoid or use cautiously, especially the antipsychotics (aka neuroleptics).

IMPORTANT NOTE: It is estimated that a high percentage of DLB patients exhibit worsening parkinsonism, sedation, immobility, or even neuroleptic malignant syndrome (NMS) after exposure to antipsychotics. NMS is a rare, life-threatening medical emergency characterized by fever, generalized rigidity and breakdown of muscle tissue that can cause renal failure and death. The heightened risk of NMS in DLB mandates that **typical or traditional antipsychotics (such as haloperidol, fluphenazine or thioridazine) should be avoided**. Atypical antipsychotics have been available for treating mental illness for 25 years and may be safer to use in patients with DLB, but only with extreme caution. Patients with PDD appear to have a lower risk of an adverse reaction to antipsychotics, but all patients with LBD should be carefully managed with any antipsychotic drug.

5.1 Goals of Care

Comprehensive, palliative management of LBD should begin at diagnosis to promote the best quality of life for the person with LBD and the family and caregivers. An early, wide-ranging discussion of symptoms and goals of treatment will proactively inform both the provider and the primary family caregiver about important future decisions.

The goals of care may change as the illness progresses due to emerging or evolving issues of safety, caregiver burden, or comorbid illness. An ongoing dialogue between the healthcare providers, patient and family about management, especially in regard to later, end-of life decisions, should occur regularly throughout the course of the illness.

5.2 First-Line Medications

5.2.1 Cognitive Impairment and Fluctuations

Acetylcholinesterase inhibitors (AChEIs): AChEIs are the current standard of care for treating cognitive and psychiatric symptoms of LBD. Three have been approved by the FDA for treatment of AD; donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). Rivastigmine is the only one of the three that is FDA-approved for treating LBD, specifically PDD. The other two are used "off label." There is no compelling evidence that any one of the three is superior to the other two in treating LBD[29].

AChEIs are generally well-tolerated by patients with LBD, but not always. For example, in a study of rivastigmine in PDD, approximately 10% of patients experienced worsening of tremor, but it was not usually clinically significant.[30] Healthcare providers and patients/caregivers must always be on guard for the development of adverse effects of any drug.

Memantine (Namenda) is another drug (with a different pharmacological mechanism of action) approved for AD but not LBD and is also used off label as an add-on therapy to AChEIs, typically in patients with more severe dementia. Only a few studies of memantine have been done in LBD, with mixed results.[31,32]

5.2.2 Parkinsonism

Levodopa is an effective and relatively safe drug for treating motor symptoms in PD; most patients with LBD respond with improvement in motor function, without side effects, as long as the dosing is kept at the lowest, most effective level.[33] However, all patients with LBD are vulnerable to the development of medication-induced behavioral or psychotic symptoms. Not everyone with LBD requires anti-parkinsonian treatment, particularly those with DLB. In fact, some patients with DLB may go years before showing signs of parkinsonism. Given the potential for adverse effects, healthcare providers should use levodopa in this setting only when symptoms are truly bothersome and should start with a low dose and titrate up slowly.

Dopamine agonists are less effective than levodopa for treating motor symptoms and are more likely to cause non-motor side effects, especially drug-induced psychosis even at low doses. Dopamine agonists may also cause excessive daytime sleepiness and swelling of the legs. Other PD medications such as amantadine, COMT inhibitors, MAO inhibitors, and anticholinergics, likewise, can induce psychosis and exacerbate cognitive impairment and should be avoided in DLB. Furthermore, dementia is a contraindication to deep brain stimulation, even when the patient is an otherwise good candidate.[34,35]

5.2.3 Behavioral Changes

The overarching goal of managing psychotic and behavioral disturbances in LBD is to improve outcome without compromising safety of the patient and others. If hallucinations (usually visual) are not frightening to the patient, even if they are considered bothersome by the family, treatment with a drug may not be needed, especially if the patient understands that the hallucinations are not real. On the other hand, delusions (a false belief held with strong conviction despite evidence to the contrary), are often socially disruptive and in most cases, should be treated, most productively by a mental health professional.

The first line intervention should be non-pharmacologic measures including evaluation for acute physical ailments that may be provoking behavioral disturbances (e.g., fecal impaction, pain, decubitus ulcers, urinary tract infection and other febrile illnesses). Medications that can potentially cause agitation, especially those with anticholinergic properties, including amantadine, certain antidepressants, and those antihistamines with significant anticholinergic effects should be reviewed for need and stopped if possible. It may be necessary to reduce or discontinue all PD medications other than low dose levodopa.

Although little evidence exists to guide specific pharmacotherapy for hallucinations and behavioral symptoms in LBD, the following background literature review should be helpful.

5.2.3.1 AChEI for Behavioral Symptoms

Deficits in the brain's supply of the neurotransmitter acetylcholine probably contribute to cognitive impairment and psychosis in LBD. Visual hallucinations may predict a favorable response to treatment with an AChEI. By comparison, a meta-analysis of 6 large trials in AD, which also causes depletion of acetylcholine in the brain, showed a small but significant benefit of AChEI treatment in decreasing neuropsychiatric symptoms. Moreover, AChEIs may selectively ameliorate psychosis and anxiety compared with other psychiatric symptoms.

A few published reports have shown behavioral improvement in patients with LBD treated with the AChEI rivastigmine. In a large multicenter trial, rivastigmine resulted in improvement by 30% from baseline in psychiatric symptoms.[36] In a comparator study of rivastigmine in patients with clinical diagnoses of DLB and AD, treatment was associated with improvement in hallucinations, anxiety, and sleep disturbances only in the DLB group.[37]

5.2.3.2 Behavioral Medications to AVOID

- **Typical antipsychotics** (neuroleptics) should always be avoided in the management of patients with LBD, especially DLB, who risk severe worsening of all symptoms, and, as mentioned above, may develop potentially fatal NMS.[38]
- **Atypical antipsychotics, especially those with high D2 receptor antagonism** (such as olanzapine and risperidone), should also be avoided due to the risk of severe neuroleptic sensitivity reactions,

neuroleptic malignant syndrome, worsening parkinsonism, somnolence and orthostatic hypotension.[39,40] Quetiapine and clozapine are two from this class of drugs that have been shown to be well tolerated in low doses for treatment of psychosis (see below).

- **Benzodiazepines and benzodiazepine-like sedative hypnotic medications (such as zolpidem)** should not be first-line agents given their risk of sedation and paradoxical agitation. (One exception is clonazepam at night for management of REM sleep behavior disorder.)
- **Opiates or tramadol** should be avoided; alternatives for pain management include nonsteroidal anti-inflammatory agents and acetaminophen.

5.2.3.3 Atypical Antipsychotics

If long-term treatment with AChEIs is ineffective, or more acute symptom control of behavior is required, it may be difficult to avoid a cautious trial of an atypical antipsychotic. When medications are needed to modify behaviors, they should be used for the shortest duration possible.

Quetiapine and clozapine are preferred when psychosis warrants drug treatment. Clozapine has been demonstrated to be effective for PD psychosis in several randomized clinical trials. However, due to the infrequent but serious risk of potentially fatal agranulocytosis (severe depression of white blood cells), and the corresponding need for intrusively frequent blood monitoring to prevent such a reaction, clozapine is not the drug of first choice. Quetiapine is a safer alternative atypical antipsychotic in PDD and DLB, typically in the dose range of 6.25 mg to 50 mg a day, although higher doses may be used if tolerated and necessary. As with any drug in this setting the low slow approach is required. Pimavanserin, now FDA-approved for the treatment of psychosis in PD[41], has not yet been studied in DLB.

Black box warning: The FDA's 'black box warning' indicates both typical and atypical antipsychotics are associated with an increased risk of mortality and morbidity in elderly patients with dementia-related psychosis. However, if used carefully according to the guidelines mentioned above, the risk of mortality is extremely low. Physicians should discuss the risks and benefits of these types of medications, so that patients with LBD and caregivers can weigh the impact of the symptoms against the potential risks associated with these medications.

5.2.3.4 Non-Pharmacological Methods to Managing Behavioral Changes

Refer to LBDA's publication, Understanding Behavioral Changes in Dementia, which can be downloaded at http://www.lbda.org/content/understanding-behavioral-changes-dementia

5.2.3.5 Emergency Room Treatment of Psychosis

Refer to LBDA's publication, Emergency Room Treatment of Psychosis, which can be downloaded at http://www.lbda.org/go/er

5.2.4 REM Sleep Behavior Disorder and Insomnia

Clonazepam has been the mainstay of medical therapy for REM sleep behavior disorder (RBD).[42] Melatonin is a safe, over-the-counter natural substance that may also offer benefit either as monotherapy without risk or in conjunction with clonazepam.

For insomnia, treatment can be attempted with antidepressants (such as trazodone or mirtazapine), low doses of benzodiazepines (such as clonazepam) or specific sedative-hypnotic agents (such as zolpidem). These medications have not been extensively studied in LBD, and worsening confusion and daytime sedation is a potential side effect of sedative-hypnotics, such as zolpidem.

5.2.5 Autonomic Dysfunction

Orthostatic hypotension (drop in blood pressure) is a common manifestation of LBD, often presenting as lightheadedness or fainting, mainly when standing. Initial management consists of simple measures such as arising slowly from a reclining or seated position, leg elevation when sitting, elastic stockings, increasing salt and fluid intake, and if possible avoiding medications that are known to exacerbate orthostasis. If simple measures fail, medications such as midodrine, fludrocortisone or the more-recently-approved droxidopa can be used.

Medications with anticholinergic activity, such as oxybutynin, tolterodine tartrate, bethanechol chloride, and propantheline, can be used to treat urinary urgency, frequency and urge incontinence. They should be used cautiously however, given their risk of exacerbating cognitive problems because of their anticholinergic properties.

Constipation can usually be treated by exercise and modifications of the daily diet to include foods with high fiber content (fruits and vegetables) and bran cereal. Laxatives, stool softeners and mechanical disimpaction may be needed.

Erectile dysfunction (ED), loss of libido and impotence in LBD is likely multifactorial. While autonomic dysfunction is a possible cause, other factors often contribute, such as depression, poor bed mobility, pain and co-morbid illnesses. Treatment can be complex, requiring a urologic and/or psychiatric consultation. Medications for ED include three inhibitors of phosphodiesterase-5 (sildenafil [Viagra], tadalfil [Cialis], and vardenafil [Levitra]), the natural substance yohimbine, or the intracavernal injectables phentolamine and prostaglandid E. If immobility in bed is a major problem, a bedtime dose of levodopa is worth a try. If mood disturbances are associated with sexual dysfunction, psychotherapy or a trial of an antidepressant can be considered, although antidepressants often cause ED.

5.3 Other Drugs to Avoid

- **Anticholinergics**, as mentioned above, may worsen cognitive impairment, confusion, and hallucinations.
- **Benzodiazepines** are best avoided unless specifically indicated (e.g. clonazepam for RBD), given their risk of sedation, increasing risk of falls, worsening cognition, and potentially paradoxical agitation.
- **Inhaled anesthetics** should be avoided when possible to minimize delirium and a decrease in functional ability.
- **OTC sleep agents** such as Tylenol or Advil PM and bladder-control medications may cause agitation. Many of these drugs contain diphenhydramine (Benadryl), an antihistamine with anticholinergic effects.

6. Referrals

6.1 Specialists

A team approach will result in the best outcomes for patients and their families. Referral to an informed neurologist is recommended for diagnosis and management of LBD symptoms; neuropsychologists may also be helpful in making a differential diagnosis. Geriatric psychiatrists may be needed to manage refractory behavioral problems.

6.2 LBDA

Caregivers need to be educated about the symptoms of LBD, standard treatment options, and how to find supportive services that may be needed over the disease course. A referral to the Lewy Body Dementia Association is recommended upon diagnosis for educational and support resources.

6.3 Legal Counsel

Early in the course of dementia, physicians can help the patient identify and share their personal goals of care and discuss advanced care planning. Healthcare providers should also encourage families to consult an attorney to ensure their legal affairs are in order, such as a will, durable power of attorney and advanced directives.

6.4 Other Referrals

A brief assessment may reveal the need for pastoral counseling or hospice care, as LBD is often life-shortening. Caregivers may also require referral for counseling due to depression or burnout.

7. Impact of LBD on the Family Caregiver

The combination of cognitive, motor and behavioral symptoms imposes significant challenges and stressors on caregivers. Education of and support for the primary caregiver is essential, and building a care team, when possible, can lessen the burden on any one individual.

7.1 Caregiver Burden

Early symptoms that are characteristic of LBD are associated with higher levels of caregiver burden, above and beyond impact of stress associated with early dementia in general.[43] Key factors in LBD caregiver burden include behavioral problems (e.g., psychosis, apathy and agitation), an impaired ability to perform activities of daily living (due to both cognitive impairment and parkinsonism), the caregiver's sense of isolation, and challenges with the diagnostic and treatment experience.

Research suggests that people with LBD may be more functionally impaired than individuals with AD with the same level of global cognitive impairment.[44] Loss of independence in ability to perform instrumental activities of daily living typically occurs early in LBD, including the inability to manage one's own medications and finances. Driving may also need to be curtailed early due to changes associated with LBD, i.e. variable levels of attention and alertness, visual hallucinations, slowed reaction time, and decreased spatial awareness.

LBD caregivers need to increasingly supervise and monitor LBD patients as particular symptoms manifest themselves or worsen, including executive impairment (i.e., difficulty planning and completing tasks), fluctuations in alertness, incontinence, intrusive hallucinations, and falls.

7.2 Diagnostic Delays

DLB caregivers often encounter significant barriers in obtaining an accurate diagnosis for their loved ones. Most see multiple physicians over more than a year before their relative is diagnosed with DLB, and more than three-quarters of persons with DLB are given a different diagnosis initially.[45]

7.3 Community-Based Services for Patients and Caregivers

The range and intensity of care required for LBD patients means that greater attention to and allocation of resources to assist LBD families are needed. One study compared resource use, cost of care, and determinants of cost of care in patients with DLB and AD. DLB patients utilized more than twice the amount of resources compared with AD patients. Specifically, DLB patients used greater resources in accommodations (long-term residential care), and required more outpatient care, informal care (measured by caregivers' lost production and lost leisure time), community services and pharmacological therapy.[46]

Among neuropsychiatric features, apathy (i.e., loss of motivation to participate in routine activities) was found to be higher in DLB patients than AD patients. In addition, the cost of care for DLB patients with apathy was almost three times as high compared with AD patients with apathy. Thus, apathy is an important behavioral feature in LBD.

7.4 Low Public Awareness

The lack of LBD awareness in the general public increases the subjective burden of LBD on families, which echoes the experience of dementia caregivers in the days before extensive public education had been provided regarding AD.[43]

7.5 Performance Worry of Caregivers

Also problematic for LBD caregivers are concerns about their own capabilities as caregivers, which is amplified due to fewer informational resources on LBD caregiving compared with those available for AD, LBD caregivers' sense of social isolation, and the challenges in finding supportive medical professionals or community services. Thus, LBD caregivers may be more concerned than other dementia caregivers about the quality of care they are providing.[43]

7.6 Monitoring for Depression and Burnout in Caregivers

Family caregivers often experience sleep deprivation, have poor eating habits, and fail to exercise enough. When it comes to their own medical care, their caregiving responsibilities may prevent them from convalescing when ill, and they often postpone or neglect to make medical appointments for themselves.

The caregiver should also be considered a patient in some respects, as the stress of being in an intense, long-term caregiver role can lead to depression, poor health and burnout, which can increase the likelihood of institutionalization of the LBD patient. Healthcare providers should urge caregivers to prioritize their own health as highly as they do that of their loved one with LBD.

Did you know?

The combination of

cognitive, motor

and

behavioral symptoms

imposes significant challenges and stressors on caregivers.

8. References

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