Dementia with Lewy Bodies: Clinical Features, Neurobiology, Diagnostic Advances, and Management Challenges

A. Abyad

Correspondence
A. Abyad, MD, MPH, MBA, DBA, AGSF
Consultant, Internal Medicine and Geriatric, Dar Al Shifa Hospital, Kuwait
Chairman, Middle-East Academy for Medicine of Aging.
President, Middle East & North Africa Association on Aging & Alzheimer's
Coordinator, Middle-East Primary Care Research Network
Coordinator, Middle-East Network on Aging
Email: aabyad@cyberia.net.lb

Received: December 2025. Accepted: January 2026; Published: March/April 2026.
Citation: Abyad A. Dementia with Lewy Bodies: Clinical Features, Neurobiology, Diagnostic Advances, and Management Challenges. World Family Medicine. March/April 2026; 24(2): 39 - 58 DOI: 10.5742/MEWFM.2026.2401027

Abstract

Dementia with Lewy bodies (DLB) is a common yet frequently underdiagnosed neurodegenerative dementia characterized by a constellation of cognitive, neuropsychiatric, motor, sleep, and autonomic features. It occupies a central position within the spectrum of synucleinopathies and shares overlapping clinical and pathological features with Alzheimer's disease (AD) and Parkinson's disease dementia (PDD). Core clinical features include fluctuating cognition, recurrent well-formed visual hallucinations, spontaneous Parkinsonism, and rapid eye movement sleep behaviour disorder (RBD), with supportive features such as autonomic dysfunction and severe sensitivity to antipsychotics. Advances in neuroimaging, particularly dopamine transporter imaging, fluorodeoxyglucose positron emission tomography, and cardiac metaiodobenzylguanidine scintigraphy, have significantly improved diagnostic accuracy. However, management remains challenging due to the narrow therapeutic window between cognitive, psychiatric, and motor symptoms, and the heightened vulnerability of patients to adverse drug effects. This narrative review synthesizes current evidence on the clinical features, neurobiology, diagnostic approaches, and management challenges of DLB, highlighting recent developments in biomarkers and emphasizing the need for individualized, multidisciplinary care strategies.

Key words:
neurodegenerative dementia, Lewy bodies, cognitive, neuropsychiatric, motor, sleep, and autonomic features,

Introduction

Dementia with Lewy bodies is the second most common neurodegenerative dementia after Alzheimer's disease, accounting for approximately 10–20% of dementia cases in older adults (McKeith et al., 2017; Walker et al., 2020). Despite its prevalence, DLB remains under-recognized and frequently misdiagnosed, most commonly as AD or other psychiatric and neurological disorders. Misdiagnosis has significant clinical consequences, particularly given the marked sensitivity of individuals with DLB to antipsychotic medications and the distinct therapeutic considerations required for managing motor and neuropsychiatric symptoms (Ballard et al., 2018).

DLB is defined neuropathologically by the presence of alpha-synuclein–containing Lewy bodies and Lewy neurites distributed throughout cortical and subcortical regions. Clinically, the disorder is characterized by a distinctive pattern of cognitive impairment, early neuropsychiatric symptoms, and Parkinsonian motor features, often accompanied by sleep and autonomic disturbances (McKeith et al., 2017). The heterogeneity of presentation and frequent coexistence of Alzheimer-type pathology further complicate diagnosis and management.

Over the past two decades, increasing recognition of prodromal features such as REM sleep behaviour disorder and advances in functional neuroimaging have refined diagnostic criteria and improved clinical detection. Nevertheless, therapeutic options remain largely symptomatic, and disease-modifying treatments are not yet available. This review aims to provide a comprehensive synthesis of the current understanding of DLB, focusing on core clinical features, hallucinations, Parkinsonism, RBD, neuroimaging and diagnostic clues, and the major challenges encountered in clinical management.

Epidemiology and Neuropathology of Dementia with Lewy Bodies

1. Epidemiology

DLB typically presents in late adulthood, with a mean age at onset between 70 and 80 years, and shows a modest male predominance (Aarsland et al., 2019). Community-based studies suggest that DLB may be underdiagnosed, with postmortem series consistently reporting higher prevalence rates than those identified clinically (Vann Jones & O'Brien, 2014). The incidence of DLB increases with age and overlaps substantially with that of both AD and PDD, contributing to diagnostic uncertainty in older populations.

Comparative epidemiological studies indicate that DLB accounts for a higher proportion of dementia cases in specialized memory clinics than in general practice settings, reflecting referral bias and the complexity of diagnosis (Walker et al., 2020). The frequent coexistence of vascular disease and Alzheimer pathology further influences clinical presentation and disease course.

2. Neuropathology

The pathological hallmark of DLB is the accumulation of misfolded alpha-synuclein within neurons, forming Lewy bodies and Lewy neurites. In contrast to Parkinson's disease, where pathology initially predominates in the brainstem, DLB is characterized by early and widespread cortical involvement, particularly in limbic and neocortical regions (Dickson et al., 2018).

Co-pathology with Alzheimer-type changes is common in DLB. Amyloid-beta plaques and tau neurofibrillary tangles are frequently observed and contribute to the severity of cognitive impairment and rate of progression (Irwin et al., 2017). This mixed pathology partly explains the overlap in clinical features between DLB and AD and underscores the biological heterogeneity of the disorder.

Neurochemical alterations in DLB include profound cholinergic deficits, often more severe than those observed in AD, which are thought to underlie prominent attentional deficits, cognitive fluctuations, and visual hallucinations (Ballard et al., 2018). Dopaminergic dysfunction in the nigrostriatal pathway contributes to Parkinsonism, while degeneration of brainstem nuclei involved in sleep regulation underlies RBD and other sleep disturbances.

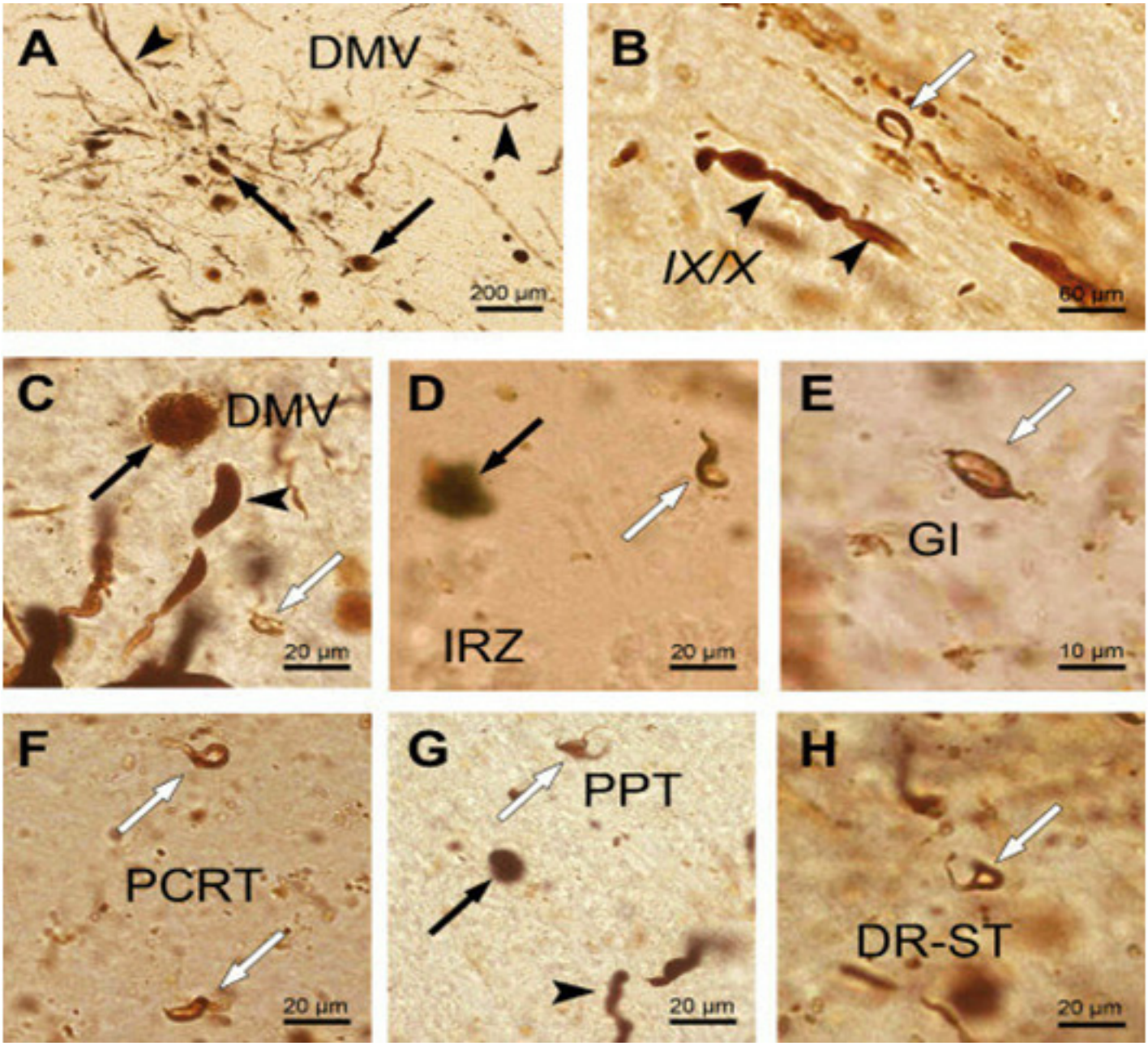


Figure 1. Neuropathological hallmark of Dementia with Lewy Bodies

Immunohistochemistry reveals intraneuronal cytoplasmic inclusions composed of misfolded α-synuclein (Lewy bodies), distributed in cortical and subcortical regions. The pathology overlaps with that seen in Parkinson's disease but is characterized by prominent cortical involvement.

Pathological Features

- α-synuclein positive inclusions
- Limbic and neocortical spread
- Frequent co-existing amyloid pathology

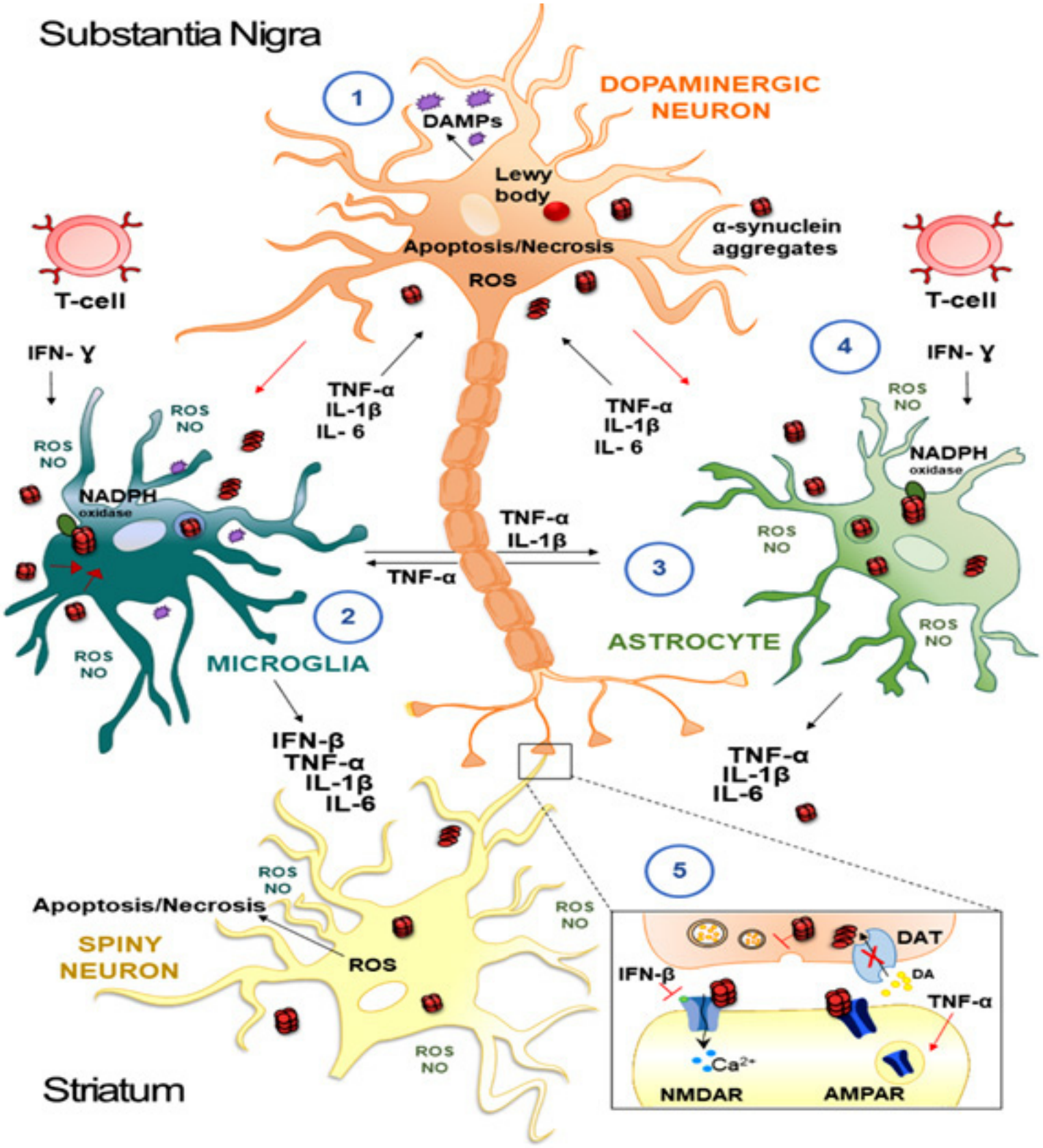


Figure 2: Neuroinflammatory and immune-mediated mechanisms contributing to dopaminergic neurodegeneration in Parkinsonian pathology

Table 1: Neuropathological Features of DLB Compared with Alzheimer's Disease and Parkinson's Disease Dementia

Feature	DLB	Alzheimer's Disease	Parkinson's Disease Dementia
Alpha-synuclein pathology	Widespread cortical and subcortical	Minimal or absent	Predominantly brainstem, later cortical
Amyloid-beta plaques	Common	Prominent	Variable
Tau pathology	Common (often mixed)	Prominent	Usually mild
Cholinergic deficit	Severe	Moderate	Moderate
Dopaminergic deficit	Present	Minimal	Marked

Source: Synthesized from McKeith et al. (2017), Dickson et al. (2018), Irwin et al. (2017)

Core Clinical Features of Dementia with Lewy Bodies

1 Cognitive Profile

The cognitive profile of DLB is distinctive and differs from that of typical AD. Early cognitive impairment in DLB is characterized by deficits in attention, executive function, and visuospatial processing, while episodic memory may be relatively preserved in the initial stages (McKeith et al., 2017; Aarsland et al., 2019). Patients often demonstrate difficulty with tasks requiring mental flexibility, visual perception, and complex problem-solving.

As the disease progresses, memory impairment becomes more prominent, particularly in individuals with significant coexisting Alzheimer pathology. However, even in later stages, attentional and visuospatial deficits often remain disproportionately severe compared with memory dysfunction, providing an important diagnostic clue (Walker et al., 2020).

2 Cognitive Fluctuations

Fluctuating cognition is a core clinical feature of DLB and refers to spontaneous, marked variations in attention and alertness. These fluctuations may manifest as episodes of staring, confusion, excessive daytime sleepiness, or transient unresponsiveness, often misinterpreted as delirium or psychiatric illness (McKeith et al., 2017).

Cognitive fluctuations are thought to reflect disruptions in cholinergic and thalamocortical networks and are strongly associated with other core features such as visual hallucinations and RBD. Their presence has significant diagnostic value, particularly when systematically assessed using validated instruments (Aarsland et al., 2019).

Table 2. Cognitive Features Distinguishing DLB from Alzheimer's Disease

Domain	DLB	Alzheimer's Disease
Attention	Early and prominent impairment	Mild in early stages
Executive function	Early impairment	Later involvement
Visuospatial ability	Markedly impaired	Moderately impaired
Memory (early disease)	Relatively preserved	Prominently impaired
Cognitive fluctuations	Common	Rare

Source: Synthesized from McKeith et al. (2017), Aarsland et al. (2019), Walker et al. (2020)

Hallucinations and Neuropsychiatric Symptoms in DLB

1 Visual Hallucinations: Phenomenology and Diagnostic Weight
Recurrent well-formed visual hallucinations are a core clinical feature of DLB and are among the most diagnostically salient symptoms because they occur early, recur, and often have stereotyped content (e.g., people, animals, children) (McKeith et al., 2017; Walker et al., 2020). Hallucinations in DLB frequently have preserved clarity and detail, distinguishing them from the less structured perceptual errors sometimes reported in Alzheimer's disease (AD) or delirium (Vann Jones & O'Brien, 2014).

Clinically, hallucinations can range from benign and non-distressing to frightening or behaviourally disruptive. Importantly, the presence of recurrent, well-formed visual hallucinations—especially when accompanied by cognitive fluctuations, Parkinsonism, or REM sleep behaviour disorder (RBD)—substantially increases the likelihood of DLB and reduces diagnostic ambiguity (McKeith et al., 2017). Hallucinations may also correlate with cholinergic deficits, occipital dysfunction, and network-level disturbances in attention and visual processing systems (Ballard et al., 2018; Taylor et al., 2020).

2 Other Hallucinations, Delusions, and Misidentification
Although visual hallucinations are most characteristic, auditory, tactile, and olfactory hallucinations can occur and may co-occur with visual phenomena (Aarsland et al., 2019). Delusions in DLB often include paranoid themes (e.g., theft, persecution) and delusional misidentification syndromes (e.g., Capgras syndrome), which can be especially challenging for caregivers and are associated with greater distress and institutionalization risk (Fénelon et al., 2000; Ballard et al., 2018).

A clinically critical feature is the high prevalence of antipsychotic sensitivity in DLB, including severe sedation, worsened Parkinsonism, neuroleptic malignant syndrome, and increased mortality risk, making routine antipsychotic use hazardous (McKeith et al., 2017; Cummings et al., 2022). Consequently, hallucinations and delusions must be managed with careful non-pharmacological triage and cautious medication selection.

3 Depression, Anxiety, Apathy, and Sleep–Mood Interactions
Neuropsychiatric symptoms extend beyond psychosis. Depression, anxiety, and apathy are common and may precede overt dementia, reflecting limbic and monoaminergic involvement (Aarsland et al., 2019; Walker et al., 2020). Sleep disruption (especially RBD and fragmented sleep) can amplify neuropsychiatric burden through fatigue, attentional fluctuations, and caregiver strain. In practice, distinguishing DLB-related symptoms from primary psychiatric disorders is essential, particularly when late-life psychosis is a presenting feature.

4 Practical Approach to Psychosis Severity
A pragmatic approach is to stratify hallucinations/delusions into:

1. Non-distressing, insight-preserved phenomena → monitor and optimize triggers (sleep, infection, medications).
2. Distressing or unsafe phenomena → intensify non-pharmacological strategies, consider cholinesterase inhibitor therapy, and only then cautious antipsychotic strategies if necessary (McKeith et al., 2017; Ballard et al., 2018).

Table 3. Neuropsychiatric Symptoms in DLB and Clinical Implications

Symptom domain	Typical features in DLB	Clinical implications
Visual hallucinations	Recurrent, well-formed, detailed images	Strong diagnostic clue; distress varies
Delusions	Paranoid themes; misidentification (e.g., Capgras)	High caregiver burden; risk of behavioural crises
Depression/anxiety	Often prominent; may precede dementia	Treat cautiously; review medication effects
Cognitive fluctuations	Episodic inattentiveness, staring spells	Can mimic delirium; important for diagnosis
Antipsychotic sensitivity	Severe reactions to dopamine blockade	Avoid typical antipsychotics; proceed cautiously

Source: Synthesized from McKeith et al. (2017), Ballard et al. (2018), Aarsland et al. (2019), Walker et al. (2020)

Parkinsonism in DLB

1 Motor Phenotype: What "Parkinsonism" Looks Like in DLB
Spontaneous Parkinsonism is a core feature of DLB and typically includes bradykinesia, rigidity, reduced facial expression, shuffling gait, postural instability, and falls (McKeith et al., 2017). Tremor may occur but is often less prominent than in idiopathic Parkinson's disease (PD), and early gait and balance impairment can be striking, contributing to functional decline and injury risk (Walker et al., 2020).

Motor features are clinically important not only for diagnosis but because they constrain treatment choices: medications that improve motor symptoms may worsen psychosis, and antipsychotics may worsen motor function (Ballard et al., 2018).

2 The "One-Year Rule" and Distinction from PDD
A standard convention in clinical practice is the one-year rule: if dementia occurs before or within one year of the onset of Parkinsonism, DLB is favoured; if dementia develops after at least one year of established PD, the diagnosis typically shifts toward Parkinson's disease dementia (PDD) (McKeith et al., 2017; Emre et al., 2007). While operationally useful, this boundary is biologically imperfect, as DLB and PDD are part of the Lewy body disease spectrum with overlapping pathology and phenotype (Irwin et al., 2017).

3 Response to Levodopa and Motor Treatment Trade-Offs
Levodopa may provide modest benefit for rigidity and bradykinesia in DLB, but responses are often less robust than in PD, and dose escalation can precipitate hallucinations or agitation (Ballard et al., 2018; Walker et al., 2020). Dopamine agonists are generally avoided because of higher risk for psychosis and impulse control symptoms in vulnerable patients.

Motor symptoms in DLB are therefore frequently managed using:

• conservative levodopa strategies (lowest effective dose),
• aggressive falls prevention,
• physical therapy and gait training,
• careful medication review to eliminate iatrogenic contributors (e.g., anticholinergics, sedatives) (McKeith et al., 2017).

Table 4. Parkinsonism in DLB vs Parkinson's Disease Dementia

Feature	DLB	Parkinson's disease dementia (PDD)
Timing of dementia vs Parkinsonism	Dementia precedes or ≤1 year from motor symptoms	Dementia occurs after established PD (>1 year)
Hallucinations/fluctuations	Often early and prominent	Common but often later
Levodopa responsiveness	Often modest	Often more robust
Antipsychotic sensitivity	High	High (but phenotype varies)
RBD/autonomic dysfunction	Common	Common

Source: Synthesized from Emre et al. (2007), McKeith et al. (2017), Irwin et al. (2017), Walker et al. (2020)

REM Sleep Behaviour Disorder in DLB

1 Clinical Characteristics and Bedside Recognition

REM sleep behaviour disorder (RBD) is a core clinical feature of DLB and is characterized by dream enactment behaviours due to loss of REM atonia, often manifesting as shouting, punching, kicking, or falling out of bed (Boeve et al., 2007; McKeith et al., 2017). RBD carries significant safety implications due to risk of injury to the patient and bed partner.

While polysomnography is the diagnostic gold standard, clinical history is highly informative, especially when combined with collateral information from family members. In DLB, RBD frequently coexists with fluctuating cognition, hallucinations, and Parkinsonism, strengthening syndromic diagnosis (McKeith et al., 2017; Postuma et al., 2019).

2 RBD as a Prodromal Marker of Synucleinopathy

Longitudinal evidence supports RBD as one of the strongest prodromal markers for alpha-synucleinopathies, including DLB. Individuals with idiopathic RBD have high long-term risk of conversion to PD, DLB, or multiple system atrophy, often over many years (Postuma et al., 2019; Iranzo et al., 2021). Clinically, this has shifted DLB from a diagnosis anchored exclusively in dementia-phase features to one increasingly recognized across a prodromal-to-established disease continuum.

3 Mechanistic Links

RBD is associated with degeneration of pontine and medullary circuits regulating REM atonia, and its association with DLB supports early brainstem involvement even when cortical symptoms dominate later (Boeve et al., 2007; Iranzo et al., 2021). Because RBD often precedes dementia by years, it can provide an early “biological clue” to synucleinopathy that is clinically useful for differential diagnosis.

Table 5. RBD in DLB: Diagnostic and Prognostic Relevance

Aspect	Key points	Clinical relevance
Symptom pattern	Dream enactment, violent movements	Injury prevention is essential
Diagnostic role	Core clinical feature of DLB	Strengthens diagnosis when combined with hallucinations/fluctuations/parkinsonism
Prodromal marker	High conversion rates to synucleinopathies	Enables early risk identification
Mechanism	Brainstem REM-atonia circuit dysfunction	Supports synucleinopathy biology

Source: Synthesized from Boeve et al. (2007), McKeith et al. (2017), Postuma et al. (2019), Iranzo et al. (2021)

Autonomic Dysfunction and Other Supportive Clinical Features

1 Autonomic Features
Autonomic dysfunction is common in DLB and includes orthostatic hypotension, constipation, urinary urgency/ incontinence, erectile dysfunction, and thermoregulatory abnormalities (McKeith et al., 2017; Walker et al., 2020). Orthostatic hypotension is particularly important clinically because it contributes to falls, syncope, cognitive "fogginess," and may exacerbate fluctuations.

2 Severe Antipsychotic Sensitivity
Severe sensitivity reactions to antipsychotic medications remain one of the most clinically dangerous aspects of DLB. Dopamine D2 blockade can precipitate profound rigidity, immobility, aspiration risk, confusion, and in rare cases life-threatening syndromes (McKeith et al., 2017; Ballard et al., 2018). This risk shapes the entire management approach to hallucinations and agitation in DLB and motivates preference for non-pharmacological measures and safer pharmacologic strategies.

3 Falls, Syncope, and Functional Decline
Falls are common and are multifactorial: Parkinsonism, autonomic dysfunction, visuospatial impairment, and medication burden contribute simultaneously. This makes DLB management inherently multidisciplinary, requiring coordinated neurologic, geriatric, psychiatric, sleep, and rehabilitation strategies (Aarsland et al., 2019; Walker et al., 2020).

Neuroimaging and Diagnostic Clues in Dementia with Lewy Bodies

Neuroimaging has become central to improving diagnostic accuracy in DLB, particularly in differentiating it from Alzheimer's disease and other dementias. Structural, functional, and molecular imaging modalities provide complementary information reflecting the underlying synucleinopathy, patterns of neurodegeneration, and neurotransmitter dysfunction characteristic of DLB.

1 Structural Neuroimaging (MRI and CT)
Conventional structural imaging using magnetic resonance imaging (MRI) or computed tomography (CT) is primarily employed to exclude alternative causes of cognitive decline such as tumours, normal pressure hydrocephalus, or extensive vascular pathology. However, structural imaging can also provide supportive diagnostic clues in DLB.
Compared with Alzheimer's disease, DLB is often characterized by relative preservation of medial temporal lobe structures, particularly the hippocampus, in early stages (Burton et al., 2012; Walker et al., 2020). This contrasts with the early and prominent hippocampal atrophy typical of AD. Cortical atrophy in DLB tends to involve posterior regions, including occipital and parietal cortices, although patterns are heterogeneous and influenced by coexisting Alzheimer pathology (Irwin et al., 2017).

Advanced MRI techniques have demonstrated increased white matter hyperintensities and microstructural changes in frontal–subcortical networks, consistent with executive dysfunction and motor impairment seen clinically (Oppedal et al., 2019). Nevertheless, structural imaging alone lacks sufficient sensitivity and specificity to reliably distinguish DLB from AD at the individual patient level.

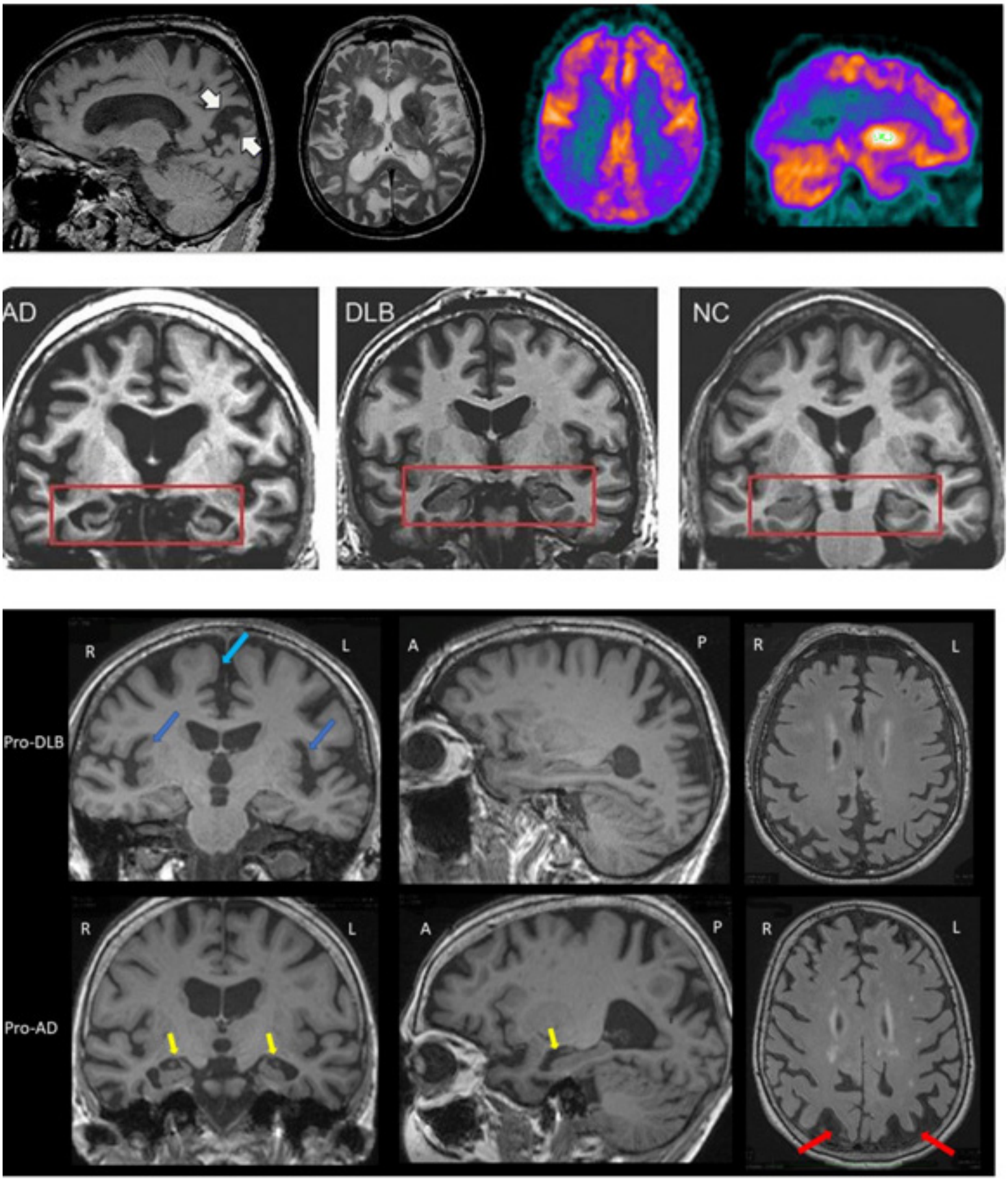


Figure 3. Structural MRI pattern in Dementia with Lewy Bodies

T1-weighted MRI typically demonstrates mild-to-moderate posterior cortical atrophy, predominantly involving the occipital and parietal lobes, with relative preservation of medial temporal structures (hippocampus) compared with Alzheimer's disease. This pattern supports differential diagnosis in early disease stages.

Key Imaging Characteristics

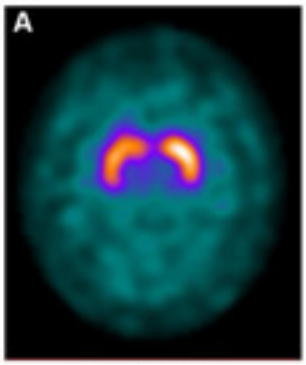
- Posterior cortical thinning (occipital > parietal)
- Less hippocampal atrophy than Alzheimer's disease
- Often mild global atrophy early in disease

2 Dopamine Transporter Imaging

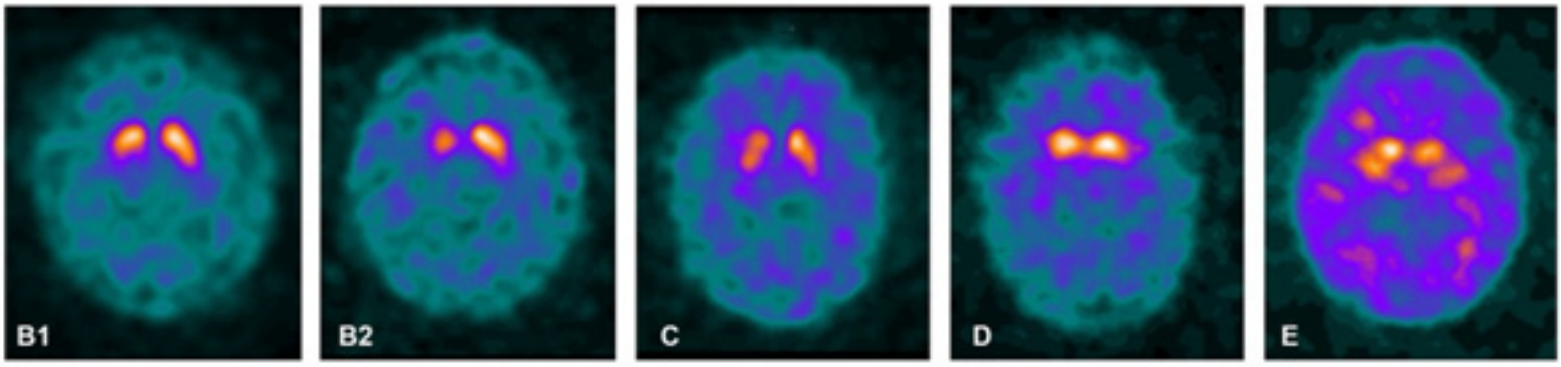
Dopamine transporter (DAT) imaging using single-photon emission computed tomography (SPECT) or positron emission tomography (PET) represents one of the most robust indicative biomarkers for DLB. Reduced striatal DAT uptake reflects nigrostriatal degeneration and is a key feature distinguishing DLB from AD (McKeith et al., 2017).

Multiple studies have demonstrated high sensitivity and specificity of DAT imaging in identifying Lewy body–related Parkinsonism, even in patients without overt motor symptoms (O'Brien et al., 2014). Importantly, DAT imaging can support a diagnosis of DLB in patients presenting primarily with cognitive or psychiatric symptoms, thereby reducing misdiagnosis and inappropriate antipsychotic exposure.

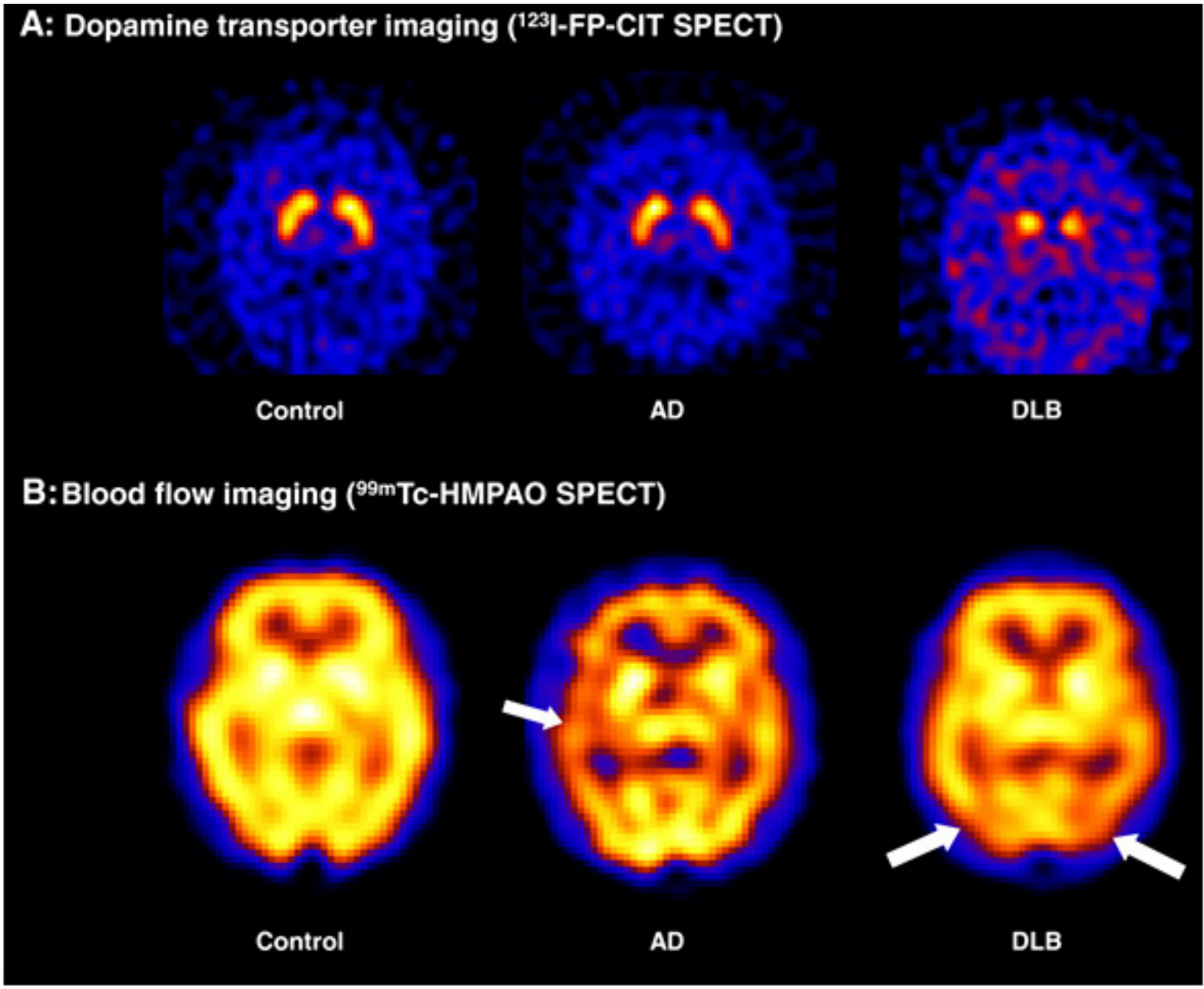
Dopamine Transporter Imaging (DaT-SPECT)



Normal scan



Examples of abnormal scans



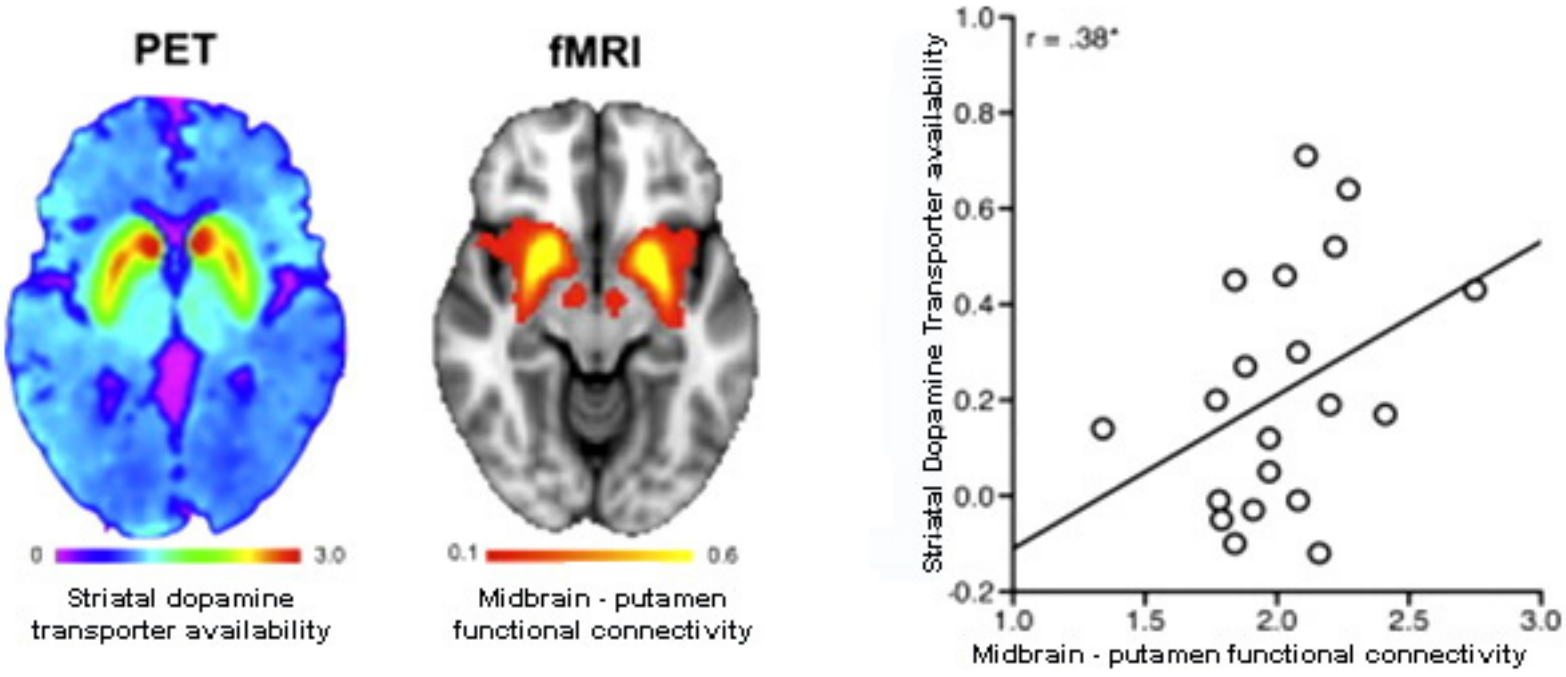


Figure 4. Dopamine transporter SPECT imaging in Dementia with Lewy Bodies.

DaT-SPECT demonstrates reduced dopamine transporter uptake in the bilateral striatum (putamen ± caudate), reflecting nigrostriatal degeneration. This finding differentiates DLB from Alzheimer's disease and overlaps pathophysiologically with Parkinson's disease.

Diagnostic Role
- Core biomarker in DLB criteria
- Supports diagnosis in patients with cognitive fluctuations + Parkinsonism
- Helps exclude pure Alzheimer's disease

3 FDG-PET and the Cingulate Island Sign
Fluorodeoxyglucose positron emission tomography (FDG-PET) reveals characteristic metabolic patterns in DLB. The most typical finding is occipital hypometabolism, often involving the primary visual cortex, which correlates with visuospatial deficits and visual hallucinations (Minoshima et al., 2001; Walker et al., 2020).

A particularly useful diagnostic feature is the cingulate island sign, defined as relative preservation of posterior cingulate metabolism compared with precuneus and cuneus regions. This pattern helps differentiate DLB from AD, where posterior cingulate hypometabolism is prominent (Lim et al., 2009). The presence of the cingulate island sign has been associated with higher diagnostic confidence and may correlate with less severe Alzheimer co-pathology.

4 Cardiac MIBG Scintigraphy
Cardiac metaiodobenzylguanidine (MIBG) scintigraphy assesses postganglionic sympathetic cardiac innervation. In DLB, reduced cardiac MIBG uptake reflects autonomic dysfunction related to alpha-synuclein pathology and serves as another indicative biomarker (McKeith et al., 2017).

MIBG scintigraphy is particularly helpful in distinguishing DLB from AD in patients with prominent autonomic symptoms or equivocal clinical features. However, its availability is limited in some regions, and results may be confounded by cardiac disease, diabetes, or certain medications (Yoshita et al., 2015).

Table 6. Neuroimaging Findings in Dementia with Lewy Bodies

Imaging modality	Typical findings in DLB	Diagnostic value
Structural MRI	Relative hippocampal preservation; posterior cortical atrophy	Supportive but low specificity
DAT SPECT/PET	Reduced striatal dopamine transporter uptake	Strong indicative biomarker
FDG-PET	Occipital hypometabolism; cingulate island sign	Differentiates DLB from AD
Cardiac MIBG	Reduced cardiac sympathetic innervation	Indicative biomarker

Source: Synthesized from Minoshima et al. (2001), Lim et al. (2009), O'Brien et al. (2014), McKeith et al. (2017), Walker et al. (2020)

Biomarkers and Diagnostic Criteria

1 Evolution of Diagnostic Criteria
The diagnostic criteria for DLB have evolved substantially, reflecting advances in clinical characterization and biomarker development. The most recent consensus criteria emphasize the integration of core clinical features with indicative biomarkers, allowing diagnosis of probable or possible DLB with greater confidence (McKeith et al., 2017).

According to current criteria, probable DLB can be diagnosed when two or more core clinical features are present, or when one core feature is accompanied by one or more indicative biomarkers. Possible DLB is diagnosed when one core feature is present without biomarkers, or when biomarkers are present in the absence of core features.

2 Cerebrospinal Fluid Biomarkers
Cerebrospinal fluid (CSF) biomarkers traditionally used in AD diagnosis, amyloid-beta, total tau, and phosphorylated tau, are increasingly applied in DLB to assess coexisting Alzheimer pathology. Many patients with DLB demonstrate reduced amyloid-beta levels with relatively lower tau concentrations compared with AD, reflecting mixed pathology (Irwin et al., 2017; Hansson et al., 2019).

CSF alpha-synuclein measurements have yielded inconsistent results due to methodological variability and overlap between diagnostic groups. However, interest has shifted toward alpha-synuclein seed amplification assays, which demonstrate markedly improved sensitivity and specificity for synucleinopathies (Shahnawaz et al., 2020).

3 Alpha-Synuclein Seed Amplification and Emerging Biomarkers
Recent advances in real-time quaking-induced conversion (RT-QuIC) and related assays allow detection of misfolded alpha-synuclein aggregates in CSF, skin, and other tissues. These techniques show promise as disease-specific biomarkers capable of identifying synucleinopathy even in prodromal stages such as RBD (Iranzo et al., 2021; McWilliam et al., 2025).

Peripheral biomarkers, including skin biopsy for phosphorylated alpha-synuclein, are also emerging as minimally invasive diagnostic tools. Blood-based biomarkers remain under investigation, with ongoing efforts to identify reliable synuclein, inflammatory, and neurodegeneration-related markers suitable for clinical use (Giannakis et al., 2025).

Table 7. Diagnostic Criteria and Biomarkers in DLB

Category	Components	Clinical relevance
Core clinical features	Fluctuations, hallucinations, Parkinsonism, RBD	Central to diagnosis
Indicative biomarkers	DAT imaging, FDG-PET patterns, MIBG scintigraphy	Increase diagnostic certainty
CSF biomarkers	Amyloid-beta, tau profiles	Identify AD co-pathology
Emerging biomarkers	Alpha-synuclein RT-QuIC, skin biopsy	Early and prodromal diagnosis

Source: Synthesized from McKeith et al. (2017), Hansson et al. (2019), Shahnawaz et al. (2020), Iranzo et al. (2021), McWilliam et al. (2025)

Differential Diagnosis of Dementia with Lewy Bodies

Accurate diagnosis of dementia with Lewy bodies is challenging because of substantial clinical overlap with other neurodegenerative and psychiatric disorders. Misdiagnosis has serious implications, particularly regarding treatment safety and prognosis. A structured differential diagnosis approach is therefore essential.

1 DLB versus Alzheimer's Disease
Alzheimer's disease is the most frequent alternative diagnosis in patients later found to have DLB. Early memory impairment, which dominates AD, may be mild or absent in early DLB, whereas attentional, executive, and visuospatial deficits are disproportionately affected in DLB (McKeith et al., 2017; Walker et al., 2020). In addition, cognitive fluctuations and well-formed visual hallucinations are uncommon in early AD and should prompt consideration of DLB.

Neuroimaging provides important clues. Relative preservation of hippocampal volume on MRI, occipital hypometabolism on FDG-PET, and the cingulate island sign favour DLB, while marked medial temporal lobe atrophy supports AD (Lim et al., 2009; Burton et al., 2012). Nevertheless, mixed pathology is common, and many patients with DLB meet biomarker criteria for concomitant AD pathology, complicating diagnostic clarity (Irwin et al., 2017).

2 DLB versus Parkinson's Disease Dementia
DLB and Parkinson's disease dementia represent phenotypic expressions of Lewy body disease and share many clinical and pathological features. The operational distinction relies on the temporal sequence of motor and cognitive symptoms, using the one-year rule (Emre et al., 2007; McKeith et al., 2017). However, from a biological perspective, this boundary is artificial, as cortical and subcortical alpha-synuclein pathology often coexist early.

Patients with DLB tend to have earlier hallucinations, cognitive fluctuations, and autonomic dysfunction, whereas patients with Parkinson's disease dementia often have a longer history of motor symptoms and greater dopaminergic responsiveness (Aarsland et al., 2019). In practice, longitudinal observation and response to therapy often clarify the diagnosis.

3 DLB versus Vascular Dementia
Vascular dementia may present with executive dysfunction, gait disturbance, and fluctuating cognition, mimicking DLB. However, vascular dementia typically demonstrates a stepwise decline, focal neurological signs, and neuroimaging evidence of extensive cerebrovascular disease (O'Brien & Thomas, 2015).

While vascular pathology frequently coexists with DLB, the presence of recurrent visual hallucinations, RBD, or abnormal dopamine transporter imaging strongly favours DLB. Careful evaluation of vascular risk factors and neuroimaging findings is required to distinguish primary vascular dementia from mixed etiologies.

4 DLB versus Primary Psychiatric Disorders
DLB is increasingly recognized as a cause of late-life psychosis and mood disturbance. Visual hallucinations, paranoia, depression, and anxiety may precede cognitive decline, leading to initial psychiatric diagnoses (Vann Jones & O'Brien, 2014). Red flags suggesting underlying DLB include new-onset psychosis after age 60, cognitive fluctuations, Parkinsonism, antipsychotic sensitivity, and RBD.

Failure to recognize DLB in psychiatric settings can expose patients to antipsychotic medications with potentially catastrophic consequences. Collaboration between psychiatry, neurology, and geriatrics is therefore critical.

Table 8. Differential Diagnosis of Dementia with Lewy Bodies

Disorder	Distinguishing features	Key differentiating clues
Alzheimer's disease	Early memory loss, fewer hallucinations	Hippocampal atrophy, AD CSF profile
Parkinson's disease dementia	Long-standing motor symptoms	Dementia develops >1 year after PD
Vascular dementia	Stepwise decline, focal deficits	Extensive cerebrovascular disease
Primary psychiatric disorders	Prominent psychosis or mood symptoms	RBD, Parkinsonism, antipsychotic sensitivity

Source: Synthesized from Emre et al. (2007), McKeith et al. (2017), Irwin et al. (2017), Walker et al. (2020)

Challenges in Management of Dementia with Lewy Bodies

Management of DLB is particularly complex due to the coexistence of cognitive impairment, neuropsychiatric symptoms, Parkinsonism, sleep disturbances, and autonomic dysfunction. Treatment strategies must balance competing symptom domains while minimizing adverse effects.

1 General Principles of Management
The cornerstone of DLB management is individualized, symptom-prioritized care delivered within a multidisciplinary framework. Non-pharmacological strategies should be optimized before pharmacological interventions, and medications should be introduced cautiously, at low doses, with close monitoring for adverse effects (McKeith et al., 2017; Ballard et al., 2018).

Polypharmacy is common and contributes significantly to morbidity. Regular medication review to eliminate anticholinergics, sedatives, and dopamine-blocking agents is essential.

2 Cognitive Symptoms
Cholinesterase inhibitors are considered first-line therapy for cognitive and neuropsychiatric symptoms in DLB. Rivastigmine and donepezil have demonstrated modest improvements in cognition, attention, hallucinations, and caregiver burden (Aarsland et al., 2019; Ballard et al., 2018). These benefits are thought to reflect the profound cholinergic deficits characteristic of DLB.

Memantine has shown mixed results, with some studies reporting modest benefits in global function and behaviour, while others demonstrate minimal impact. Its use may be considered on an individual basis, particularly in later disease stages (Stinton et al., 2015).

3 Management of Psychosis
Psychosis in DLB represents one of the most challenging therapeutic domains. Non-distressing hallucinations may not require treatment. When intervention is necessary due to distress or safety concerns, cholinesterase inhibitors should be optimized first, as they may reduce hallucinations without worsening motor symptoms (Ballard et al., 2018).
Antipsychotics should be avoided whenever possible. If absolutely necessary, agents with minimal dopamine D2 antagonism should be used at the lowest effective dose, with close monitoring for sedation, rigidity, confusion, and autonomic instability (Cummings et al., 2022). Typical antipsychotics are contraindicated due to high risk of severe reactions.

4 Management of Parkinsonism
Levodopa may be used cautiously to treat disabling motor symptoms, but benefits are often limited, and neuropsychiatric side effects are common (Walker et al., 2020). Dopamine agonists, anticholinergics, and amantadine are generally avoided due to risk of hallucinations and cognitive worsening.

Non-pharmacological strategies, including physical therapy, balance training, and falls prevention programs, are essential components of motor management.

5 Sleep and Autonomic Dysfunction
RBD is commonly treated with environmental safety measures, melatonin, or low-dose clonazepam, balancing efficacy with fall and cognitive risks (Postuma et al., 2019). Autonomic symptoms such as orthostatic hypotension require non-pharmacological measures first, including hydration, compression garments, and positional strategies, with pharmacological treatment reserved for refractory cases.

Table 9. Pharmacological Management in DLB: Benefits and Risks

Symptom domain	Treatment options	Key risks
Cognitive impairment	Cholinesterase inhibitors	Bradycardia, gastrointestinal effects
Psychosis	Cholinesterase inhibitors; cautious antipsychotic use	Severe sensitivity reactions
Parkinsonism	Low-dose levodopa	Worsening hallucinations
RBD	Melatonin, clonazepam	Sedation, falls
Autonomic dysfunction	Supportive measures ± medication	Hypotension, polypharmacy

Source: Synthesized from McKeith et al. (2017), Ballard et al. (2018), Aarsland et al. (2019), Cummings et al. (2022)

Disease Course, Prognosis, and Quality of Life in Dementia with Lewy Bodies

1 Natural History and Progression Patterns

Dementia with Lewy bodies is characterized by a progressive and often fluctuating clinical course. Compared with Alzheimer's disease, DLB generally exhibits a more rapid functional decline, earlier neuropsychiatric burden, and greater variability in day-to-day cognitive performance (Aarsland et al., 2019; Walker et al., 2020). Cognitive deterioration typically evolves from early attentional and visuospatial deficits toward more global impairment, with memory involvement increasing over time, particularly in the presence of concomitant Alzheimer pathology (Irwin et al., 2017).

Motor symptoms, including Parkinsonism and gait instability, often progress in parallel with cognitive decline, contributing to falls, immobility, and loss of independence. REM sleep behaviour disorder, autonomic dysfunction, and psychosis may intensify as the disease advances, further complicating management and accelerating institutionalization (McKeith et al., 2017).

2 Survival and Mortality

Multiple cohort studies indicate that individuals with DLB have shorter survival compared with those diagnosed with Alzheimer's disease, even after adjustment for age and comorbidity burden (Mueller et al., 2017; Oesterhus et al., 2014). Median survival from diagnosis typically ranges between 5 and 8 years, although variability is considerable and influenced by factors such as age at onset, comorbid vascular disease, severity of autonomic dysfunction, and exposure to antipsychotic medications.

Causes of death in DLB are often multifactorial and include aspiration pneumonia, infections, falls and fractures, cardiovascular complications, and consequences of severe autonomic instability (Aarsland et al., 2019). Neuroleptic sensitivity reactions have also been implicated in excess mortality, underscoring the importance of cautious pharmacological management (Ballard et al., 2018).

3 Quality of Life and Functional Outcomes

Quality of life (QoL) in DLB is frequently compromised early in the disease course. Compared with Alzheimer's disease, patients with DLB report poorer QoL scores, driven largely by hallucinations, depression, sleep disturbances, and motor disability rather than cognitive impairment alone (Boström et al., 2007; Oesterhus et al., 2014).

Functional decline in DLB is accelerated by the interaction of cognitive fluctuations, visuospatial impairment, and Parkinsonism, which together impair activities of daily living and increase reliance on caregivers. Loss of driving ability, frequent falls, and sleep-related injuries further erode independence and psychosocial well-being.

Table 10. Disease Course and Prognostic Features in DLB

Domain	Typical features	Prognostic implications
Cognitive decline	Early attentional and visuospatial deficits	Faster functional loss
Motor progression	Early gait instability, rigidity	Increased fall and injury risk
Neuropsychiatric burden	Hallucinations, depression, fluctuations	Poorer quality of life
Autonomic dysfunction	Orthostatic hypotension, syncope	Increased morbidity and mortality
Survival	Shorter than AD on average	Influenced by comorbidities and treatment

Source: Synthesized from Oesterhus et al. (2014), Mueller et al. (2017), Aarsland et al. (2019), Walker et al. (2020)

Caregiver Burden and Health System Impact

1 Caregiver Burden and Psychosocial Stress

Caregiver burden in DLB is consistently higher than in Alzheimer's disease and other dementias, largely due to the complexity and unpredictability of symptoms (Leggett et al., 2011). Caregivers must manage fluctuating cognition, distressing hallucinations, sleep disruption from RBD, motor instability, and frequent medical crises, often simultaneously.

Visual hallucinations and delusions are particularly distressing for caregivers and are strongly associated with caregiver depression, anxiety, and burnout (Leggett et al., 2011; Boström et al., 2007). Night-time behaviours related to RBD and sleep fragmentation further disrupt caregiver sleep and contribute to physical and emotional exhaustion.

2 Health Care Utilization and Costs

Patients with DLB have higher rates of hospitalization, emergency department visits, and institutionalization compared with those with Alzheimer's disease (Mueller et al., 2017). Falls, syncope, delirium, medication adverse effects, and infections are common drivers of acute care utilization.

The economic burden of DLB extends beyond direct medical costs to include informal caregiving, loss of productivity, and long-term care placement. Delayed or incorrect diagnosis may exacerbate costs by leading to inappropriate treatments, repeated investigations, and preventable adverse events, particularly antipsychotic-related complications (McKeith et al., 2017).

3 Importance of Education and Multidisciplinary Care

Education of caregivers and health professionals is critical to improving outcomes in DLB. Understanding symptom fluctuations, medication sensitivities, and non-pharmacological strategies empowers caregivers to manage symptoms more effectively and may reduce crisis-driven health care utilization. Multidisciplinary models incorporating neurology, geriatrics, psychiatry, sleep medicine, rehabilitation, and social support are increasingly recognized as best practice for DLB care (Aarsland et al., 2019).

Table 11. Caregiver and Health System Impact of DLB

Aspect	Key challenges	Implications
Caregiver burden	Hallucinations, sleep disruption, falls	Increased stress and burnout
Hospitalization	Falls, delirium, adverse drug effects	Higher acute care utilization
Long-term care	Early institutionalization	Increased societal costs
Education gaps	Low awareness among clinicians	Delayed diagnosis and mismanagement

Source: Synthesized from Boström et al. (2007), Leggett et al. (2011), Mueller et al. (2017), Aarsland et al. (2019)

Future Directions and Emerging Therapies

1 Early and Prodromal Identification
A major focus of current research is the identification of DLB at prodromal or pre-dementia stages, particularly among individuals with REM sleep behaviour disorder, mild cognitive impairment with Lewy body features, or subtle Parkinsonism (Postuma et al., 2019; Iranzo et al., 2021). Early identification is essential for timely counseling, risk mitigation, and eventual deployment of disease-modifying therapies.

The integration of clinical features with biomarkers such as dopamine transporter imaging, alpha-synuclein seed amplification assays, and multimodal neuroimaging holds promise for improving diagnostic accuracy and staging (Shahnawaz et al., 2020; McWilliam et al., 2025).

2 Disease-Modifying and Targeted Therapies
Despite advances in symptomatic management, no disease-modifying therapies for DLB are currently available. Therapeutic strategies targeting alpha-synuclein aggregation, propagation, and clearance are under active investigation, including immunotherapies and small-molecule inhibitors (Cummings et al., 2022).

Given the frequent coexistence of Alzheimer pathology in DLB, combination approaches addressing both synuclein and amyloid/tau pathways may be necessary. Precision medicine frameworks that stratify patients based on biomarker profiles and dominant symptom domains represent a promising future direction.

3 Digital Health and Personalized Care
Wearable technologies and digital biomarkers offer opportunities to monitor motor function, sleep, and autonomic symptoms longitudinally in real-world settings. These tools may facilitate earlier detection of symptom progression, personalized treatment adjustments, and improved clinical trial endpoints (Walker et al., 2020).

Table 12. Emerging Directions in DLB Research and Care

Area	Focus	Potential impact
Prodromal diagnosis	RBD, MCI-LB, biomarkers	Earlier intervention
Alpha-synuclein therapies	Immunotherapy, aggregation inhibitors	Disease modification
Multimodal biomarkers	Imaging + CSF + peripheral markers	Improved diagnostic precision
Digital health	Wearables, remote monitoring	Personalized care and trials

Source: Synthesized from Postuma et al. (2019), Shahnawaz et al. (2020), Cummings et al. \(2022), McWilliam et al. (2025)

Conclusion

Dementia with Lewy bodies represents a complex, multisystem neurodegenerative disorder situated at the intersection of cognitive, motor, neuropsychiatric, sleep, and autonomic dysfunction. Despite being the second most common neurodegenerative dementia, DLB remains underdiagnosed and frequently misclassified, often as Alzheimer's disease, Parkinson's disease dementia, or primary psychiatric illness. This diagnostic ambiguity carries substantial clinical consequences, particularly in light of the profound sensitivity of individuals with DLB to antipsychotic medications and the delicate balance required in managing cognitive, motor, and behavioural symptoms.

The clinical phenotype of DLB is distinguished by fluctuating cognition, recurrent well-formed visual hallucinations, spontaneous Parkinsonism, and REM sleep behaviour disorder, supported by autonomic dysfunction, severe neuroleptic sensitivity, and recurrent falls. Advances in neuroimaging—including dopamine transporter imaging, FDG-PET with identification of occipital hypo-metabolism and the cingulate island sign, and cardiac MIBG scintigraphy, have substantially improved diagnostic confidence. Emerging biomarkers, particularly alpha-synuclein seed amplification assays in cerebrospinal fluid and peripheral tissues, offer the promise of earlier and more specific diagnosis across the prodromal-to-dementia continuum.

Management of DLB remains challenging and largely symptomatic. Cholinesterase inhibitors represent the cornerstone of cognitive and neuropsychiatric treatment, while management of psychosis, Parkinsonism, sleep disturbance, and autonomic dysfunction requires cautious, individualized strategies to minimize harm. The disease course is often more aggressive than Alzheimer's disease, with higher caregiver burden, greater health care utilization, and reduced quality of life.

Future progress in DLB care will depend on improved early recognition, integration of multimodal biomarkers, development of disease-modifying therapies targeting alpha-synuclein pathology, and adoption of multidisciplinary, patient-centered

care models. As understanding of the biological and clinical heterogeneity of DLB deepens, there is increasing opportunity **to shift from reactive symptom management toward proactive, precision-based approaches that improve outcomes for patients and caregivers alike.**

References

Aarsland, D., Ballard, C., Halliday, G., & McKeith, I. (2019). Dementia with Lewy bodies. Nature Reviews Disease Primers, 5, 1–20.

Ballard, C., Aarsland, D., McKeith, I., O'Brien, J., Gray, A., Cormack, F., … Perry, R. (2001). Fluctuations in attention: PD dementia vs DLB. Neurology, 56(7), 889–894.

Ballard, C., O'Brien, J., Taylor, J. P., & McKeith, I. (2018). Management of dementia with Lewy bodies. Lancet Neurology, 17(2), 157–169.

Boeve, B. F., Silber, M. H., Ferman, T. J., Lucas, J. A., Parisi, J. E., & Dickson, D. W. (2007). REM sleep behavior disorder and degenerative dementia. Neurology, 69(9), 944–951.

Boström, F., Jönsson, L., Minthon, L., & Londos, E. (2007). Patients with DLB have more impaired quality of life than AD. International Journal of Geriatric Psychiatry, 22(6), 525–531.

Burton, E. J., Barber, R., Mukaetova-Ladinska, E. B., Robson, J., Perry, R. H., Jaros, E., … O'Brien, J. T. (2012). Medial temporal lobe atrophy in DLB. Journal of Neurology, Neurosurgery & Psychiatry, 83(7), 690–695.

Cummings, J., Lee, G., Nahed, B., Kambar, M. E., Zhong, K., Fonseca, J., & Taghva, K. (2022). Alzheimer's disease drug development pipeline. Alzheimer's & Dementia, 8, e12295.

Dickson, D. W., Heckman, M. G., Murray, M. E., Soto, A. I., Walton, R. L., Diehl, N. N., … Josephs, K. A. (2018). Neuropathology of DLB. Acta Neuropathologica, 135(4), 611–624.

Emre, M., Aarsland, D., Brown, R., Burn, D. J., Duyckaerts, C., Mizuno, Y., … Dubois, B. (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. Movement Disorders, 22(12), 1689–1707.

Fénelon, G., Mahieux, F., Huon, R., & Ziégler, M. (2000). Hallucinations in Parkinson's disease. Brain, 123(4), 733–745.

Giannakis, M., Montine, T. J., & Trojanowski, J. Q. (2025). Fluid biomarkers in synucleinopathies. Lancet Neurology, 24(1), 45–58.

Hansson, O., Seibyl, J., Stomrud, E., Zetterberg, H., Trojanowski, J. Q., Bittner, T., … Mattsson, N. (2019). CSF biomarkers in neurodegeneration. Neurology, 92(13), e1412–e1421.

Iranzo, A., Santamaria, J., & Tolosa, E. (2021). Idiopathic RBD and neurodegeneration. Lancet Neurology, 20(4), 278–288.

Irwin, D. J., Lee, V. M. Y., & Trojanowski, J. Q. (2017). Parkinson's disease dementia and DLB. Cold Spring Harbor Perspectives in Medicine, 7(4), a024307.

Leggett, A. N., Zarit, S., Taylor, A., & Galvin, J. E. (2011). Stress and burden in DLB caregivers. Gerontologist, 51(1), 76–85.

Lim, S. M., Katsifis, A., Villemagne, V. L., Best, R., Jones, G., Saling, M., … Rowe, C. C. (2009). The cingulate island sign. Journal of Nuclear Medicine, 50(10), 1638–1645.

McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J. P., Weintraub, D., … Kosaka, K. (2017). Diagnosis and management of DLB: Fourth consensus report. Neurology, 89(1), 88–100.

McWilliam, M., Kraus, A., & Soto, C. (2025). Alpha-synuclein RT-QuIC in clinical practice. Nature Medicine, 31, 112–121.

Minoshima, S., Foster, N. L., & Sima, A. A. (2001). FDG-PET in DLB. Annals of Neurology, 49(1), 78–83.

Mueller, C., Ballard, C., Corbett, A., & Aarsland, D. (2017). Survival in DLB vs AD. BMJ Open, 7, e013504.

O'Brien, J. T., & Thomas, A. (2015). Vascular dementia. Lancet, 386(10004), 1698–1706.

O'Brien, J. T., McKeith, I. G., Walker, Z., Tatsch, K., Booij, J., Darcourt, J., … Pogarell, O. (2014). Diagnostic accuracy of DAT imaging. Lancet Neurology, 13(10), 1050–1058.

Oesterhus, R., Soennesyn, H., Rongve, A., Ballard, C., Aarsland, D., & Vossius, C. (2014). Survival in DLB. Journal of Neurology, Neurosurgery & Psychiatry, 85(3), 320–325.

Postuma, R. B., Iranzo, A., Hu, M., Högl, B., Boeve, B. F., Manni, R., … Berg, D. (2019). Risk of synucleinopathy in RBD. Lancet Neurology, 18(9), 1–11.

Shahnawaz, M., Tokuda, T., Waragai, M., Mendez, N., Ishii, R., Trenkwalder, C., … Soto, C. (2020). Alpha-synuclein RT-QuIC in CSF. Acta Neuropathologica, 139(3), 415–428.

Stinton, C., McKeith, I., Taylor, J. P., Lafortune, L., Mioshi, E., Mak, E., … O'Brien, J. T. (2015). Pharmacological management of DLB. Cochrane Database of Systematic Reviews, 3, CD010351.

Taylor, J. P., McKeith, I. G., Burn, D. J., Boeve, B. F., Weintraub, D., Bamford, C., & Thomas, A. J. (2020). New evidence on the management of DLB. Lancet Neurology, 19(2), 157–169.

Vann Jones, S. A., & O'Brien, J. T. (2014). The prevalence and incidence of DLB. Age and Ageing, 43(3), 314–321.

Walker, Z., Possin, K. L., Boeve, B. F., & Aarsland, D. (2015). Lewy body dementias. Lancet, 386(10004), 1683–1697.

Walker, Z., McKeith, I., & O'Brien, J. (2020). Imaging in DLB. Journal of Neurology, Neurosurgery & Psychiatry, 91(6), 638–646.