Redefining Dementia with Lewy Bodies: From Clinical Diagnosis to Targeted Therapies

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DESPITE being the second most common degenerative dementia after Alzheimer's disease, dementia with Lewy bodies (DLB) remains underrecognised, and disease-modifying treatments are not currently available. Experts at the European Academy of Neurology (EAN) Congress 2026 explored the evolving understanding of DLB, including advances in diagnosis, emerging biological definitions of disease, and the expanding therapeutic landscape. The session, held jointly with the European Section of the Movement Disorder Society, was chaired by Irena Rektorová, Masaryk University, Brno, Czechia; and Dag Aarsland, King's College London, UK.

REFINING THE DIAGNOSIS OF DEMENTIA WITH LEWY BODIES

Opening the session, Evelien Lemstra, Amsterdam University Medical Centres, the Netherlands, highlighted the challenges associated with recognising DLB, a heterogeneous disorder with diverse clinical presentations. Although currently incurable, many symptoms can be treated, and early diagnosis remains essential to enable appropriate management. She emphasised that patients with DLB experience poorer outcomes compared with those with Alzheimer's disease, including higher healthcare costs and increased likelihood of nursing home admission,[1] raising the possibility that earlier recognition and intervention could improve future outcomes.

Lemstra explained that DLB is characterised by α-synuclein pathology, although Alzheimer's disease-related pathology is also concurrently present in a substantial proportion of patients. Unlike Alzheimer's disease, where memory and language impairment are often prominent, DLB is typically associated with deficits in executive function, visuospatial abilities, and attention.

In 2017, the DLB Consortium published a refined diagnostic criterion, which distinguishes clearly between clinical features and diagnostic biomarkers.[2] The clinical diagnostic framework is based on characteristic clinical features, with the 'central feature' being dementia.[2] In addition, 'core features' include cognitive fluctuations, recurrent visual hallucinations, parkinsonism, and rapid eye movement sleep behaviour disorder (RBD). Cognitive fluctuations may involve marked variations in alertness and attention, with patients appearing relatively well at some times and markedly drowsy or confused at others. Visual hallucinations are often an early and distinctive feature of DLB, while parkinsonism may be absent at disease onset in many patients. Lemstra highlighted that many patients with DLB are unable to tolerate conventional antipsychotic treatments due to neuroleptic sensitivity.

RBD, which involves abnormal behaviours during the dream phase of sleep, is also considered a characteristic feature of DLB. Additional 'supportive features' described in the diagnostic criteria include postural instability, syncope, autonomic dysfunction, and psychiatric symptoms.

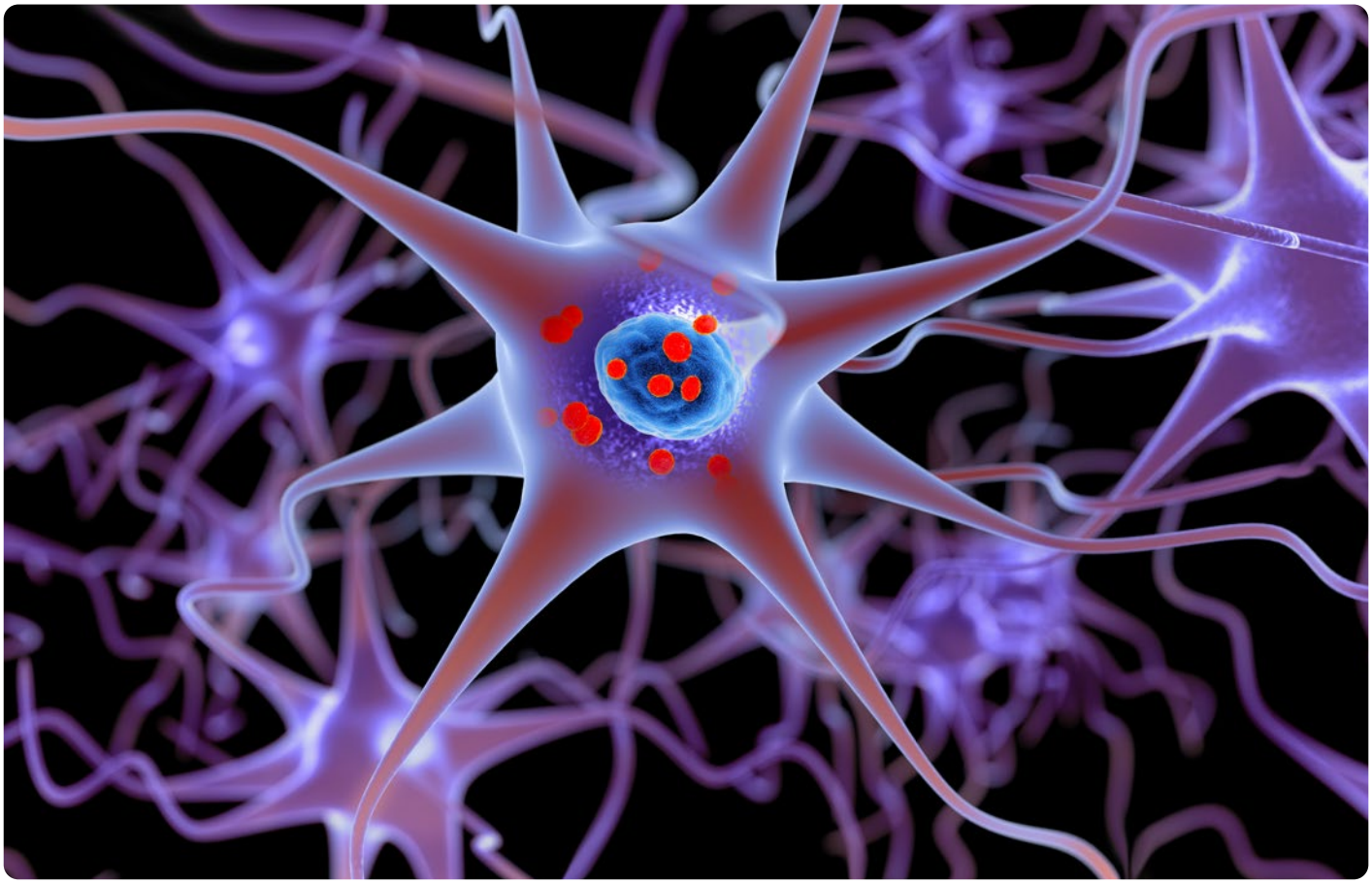
The diagnostic criteria also incorporate indicative biomarkers, including abnormalities on dopamine transporter imaging (DATScan; GE HealthCare, Chicago, Illinois, USA), myocardial scintigraphy using metaiodobenzylguanidine (MIBG), and polysomnography-confirmed RBD. Supportive biomarkers include relative preservation of medial temporal structures compared with Alzheimer's disease, characteristic findings on fluorodeoxyglucose PET, including the cingulate island sign, and early electroencephalographic slowing.

A key clinical challenge is distinguishing DLB from Parkinson's disease dementia, given the clinical overlap between these disorders. The 1-year rule remains central to this distinction: when dementia occurs before or within 1 year of the onset of parkinsonism, the diagnosis is DLB, whereas Parkinson's disease dementia refers to dementia developing after Parkinson's disease is well-established.

TOWARDS A BIOLOGICAL DEFINITION OF LEWY BODY DISEASE

Lemstra explained that Lewy body disease encompasses many phenotypes, including DLB, Parkinson's disease, Parkinson's disease mild cognitive impairment, Parkinson's disease dementia, prodromal Parkinson's disease, mild cognitive impairment with Lewy bodies, prodromal DLB, and idiopathic RBD. As these phenotypes are mainly clinically defined, there is substantial overlap in symptomology, and Lemstra explained that this can be confusing for patients. Therefore, there has been a shift towards biologically defined disease. Rather than defining disease solely by clinical presentation, biological classifications aim to identify the underlying protein pathology, regardless of whether clinical symptoms are present.

A major development enabling this transition has been the ability to detect α-synuclein pathology using real-time quaking-induced conversion, also known as a seeding amplification assay. This technique detects the aggregation properties of



α-synuclein and has demonstrated high sensitivity and specificity for Lewy body diseases in selected cohorts.[3] Although cerebrospinal fluid currently provides the strongest results, α-synuclein detection in skin samples and olfactory mucosa may provide less invasive diagnostic approaches in the future.

In 2024, two proposed biological frameworks for Lewy body disease were published: the Neuronal Alpha-Synuclein Disease Integrated Staging System,[4] and the SynNeurGe research diagnostic criteria.[5] This first framework proposes that α-synuclein aggregation occurs first, followed by neurodegeneration, clinical symptoms, and functional impairment. The two main anchors for the staging system are α-synuclein pathology measured by real-time quaking-induced conversion and dopaminergic degeneration measured by DATScan. In comparison, SynNeurGe focuses on biological disease states rather than stages. It incorporates genetic status, α-synucleinopathy, neurodegeneration, and clinical symptoms to classify patients according to underlying biology. Importantly, neither of these frameworks is yet validated for clinical practice, and is instead used as research criteria to facilitate trial design.

Important uncertainties remain, including whether pathological processes occur in a consistent sequence, how biomarker changes relate to clinical progression, and whether individuals with biological evidence of α-synuclein pathology but no symptoms should be considered patients or individuals at risk of future disease. Furthermore, Lemstra noted that Alzheimer's co-pathology contributes to disease progression and survival in DLB,[6] highlighting the importance of incorporating co-pathologies into future biological classification frameworks.

CURRENT TREATMENTS AND THE SEARCH FOR DISEASE-MODIFYING THERAPIES

Aarsland highlighted the limited evidence base for managing DLB. Currently, the strongest evidence supports cholinesterase inhibitors, with rivastigmine and donepezil demonstrating beneficial effects in DLB. These treatments are generally well tolerated and remain the mainstay of therapy, although the supporting studies were conducted approximately 2 decades ago, highlighting the need for new approaches.

Psychosis remains a major treatment challenge. Evidence for antipsychotic use specifically in DLB is limited, although quetiapine and clozapine appear least likely to worsen parkinsonism, according mostly to anecdotal evidence, Aarsland explained.

Beyond symptomatic therapies, multiple disease-modifying strategies are under investigation. Given the central role of α-synuclein pathology in DLB, several approaches aim to reduce α-synuclein production, prevent aggregation, limit its spread, or enhance degradation. However, robust evidence for these strategies remains limited.

Nevertheless, Aarsland highlighted several Phase II trials investigating different therapeutic approaches, including servimecine (CT1812), neflamapimod, and nilotinib, which have generated encouraging early findings. For example, servimecine was investigated in 130 patients with mild-to-moderate Lewy body disease over 6 months.[7] The study met its primary endpoints of safety and tolerability, with encouraging numerical improvements across behavioural, functional, cognitive, and movement-related measures, although no effects were observed on plasma biomarkers.

Another study highlighted by Aarsland was a Phase II trial of nilotinib involving 43 patients with DLB over 6 months.[8] Although primarily designed to assess pharmacokinetics, the study reported improvements in several clinical and biomarker secondary measures, including

a reduced number of falls, improved dopamine and Alzheimer's-related biomarkers, and improved cognition compared with placebo.

THE FUTURE OF DLB RESEARCH

Aarsland noted that there are currently around 40 active trials in Lewy body disease, with 11 including DLB populations. However, clinical trials remain challenging due to the lack of a universally accepted outcome measure. Symptoms vary considerably between patients, making it difficult to detect treatment effects. Initiatives such as the Core Outcome Set for DLB[9] and the Lewy Body Dementia-Domain Rating Scale (LBD-DRS)[10] aim to address these limitations. Biomarkers may also transform future trials.

α-synuclein seeding amplification assays could support patient stratification, while quantitative measures of α-synuclein signal may eventually provide outcome measures for disease-modifying therapies.

Concluding the session, Aarsland emphasised that the field is moving towards biologically based disease classification, where patients may ultimately be characterised by their individual patterns of protein pathology rather than traditional clinical diagnoses. This could enable personalised combinations of therapies targeting specific pathological processes. Although DLB research remains behind that of Alzheimer's disease and Parkinson's disease, increasing trial activity and advances in biomarkers offer the prospect of more targeted treatments in the future.

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