Dementia with Lewy Bodies: Impact of Co-pathologies and Implications for Clinical Trial Design

Jon B. Toledo, MD, Ph.D.[1], Carla Abdelnour, MD[2], Rimona S. Weil, MBBS, Ph.D.[3], Daniel Ferreira, Ph.D.[4], Federico Rodriguez-Porcel, MD[5], Andrea Pilotto, MD, Ph.D.[6], Kathryn A. Wyman-Chick, PsyD[7], Michel J. Grothe, Ph.D.[8], Joseph PM Kane, MD[9], Angela Taylor[10], Arvid Rongve, MD[11], Sonja Scholz, MD, Ph.D.[12], James B. Leverenz, MD[13], Bradley F. Boeve, MD[14], Dag Aarsland, MD[15], Ian G. McKeith, MD[16], Simon Lewis, MD[17], Iracema Leroi, MD[18], John P. Taylor, MD[19] on behalf of the ISTAART Lewy body dementias Trial Methods Working Group

[1]Nantz National Alzheimer Center, Stanley H. Appel Department of Neurology, Houston Methodist Hospital, Houston, Texas, USA

[2]Fundació ACE. Barcelona Alzheimer Treatment and Research Center, Barcelona, Spain; Universitat Autónoma de Barcelona, Barcelona, Spain

[3]Dementia Research Centre, University College London, UK; Wellcome Centre for Human Neuroimaging, University College London, UK; Movement Disorders Consortium, National Hospital for Neurology and Neurosurgery, London, UK

[4]Division of Clinical Geriatrics, Center for Alzheimer Research, Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet, Stockholm, Sweden; Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA

[5]Department of Neurology, Medical University of South Carolina, Charleston, South Carolina, USA

[6]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy; Parkinson's Disease Rehabilitation Centre, FERB ONLUS-S. Isidoro Hospital, Trescore Balneario (BG), Italy

[7]HealthPartners Center for Memory and Aging and Struthers Parkinson's Center, Saint Paul, Minnesota, USA

[8]Unidad de Trastornos del Movimiento, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Spain

[9]Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom

[10]Lewy Body Dementia Association, Lilburn, GA, United States

[11]Department of Research and Innovation, Helse Fonna, Haugesund Hospital, Haugesund, Norway and The University of Bergen, Institute of Clinical Medicine (K1), Bergen, Norway

[12]Neurodegenerative Diseases Research Unit, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA; Department of Neurology, Johns Hopkins University Medical Center, Baltimore, MD, USA

[13]Lou Ruvo Center for Brain Health, Cleveland Clinic, Cleveland, OH, United States

[14]Department of Neurology and Center for Sleep Medicine, Mayo Clinic, Rochester, MN. USA

[15]Department of Old Age Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, London, UK

[16]Newcastle University Translational and Clinical Research Institute (NUTCRI,) Newcastle upon Tyne, UK

[17]ForeFront Parkinson's Disease Research Clinic, 100 Mallett Street, Brain and Mind Centre, School of Medical Sciences, University of Sydney, Camperdown, NSW 2050, Australia

[18]Trinity College Dublin, Global Brain Health Institute, Dublin, Ireland

[19]Translational and Clinical Research Institute, Newcastle University, UK

Abstract

Dementia with Lewy bodies (DLB) is clinically defined by the presence of visual hallucinations, fluctuations, REM sleep behavioral disorder, and parkinsonism. Neuropathologically, it is characterized by the presence of Lewy pathology. However, neuropathological studies have demonstrated the high prevalence of coexistent Alzheimer's disease, TDP-43, and cerebrovascular pathologic cases. Due to their high prevalence and clinical impact on DLB individuals, clinical trials should account for these co-pathologies in their design and selection and the interpretation of biomarkers values and outcomes. Here, we discuss the frequency of the different co-pathologies in DLB and their cross-sectional and longitudinal clinical impact. We then evaluate the utility and possible applications of disease-specific and disease non-specific biomarkers and how co-pathologies can impact these biomarkers. We propose a framework for integrating multi-modal biomarker fingerprints and step-wise selection and assessment of DLB individuals for clinical trials, monitoring target engagement, and interpreting outcomes in the setting of co-pathologies.

Keywords

Dementia with Lewy bodies; Lewy body dementia; α-synuclein; dementia; parkinsonism; PET; MRI; cerebrospinal fluid; neurodegeneration; clinical trials

Introduction

The principle of parsimony guides clinical diagnosis. In neurodegenerative disorders, the clinical signs and symptoms have previously been correlated with neurodegeneration in discrete and selectively vulnerable nervous system regions. A prior prevailing view has been that a combination of distinctive clinical and brain changes is characteristic of singular neurodegenerative processes [1]. However, neuropathological studies have challenged this concept, showing that cognitively impaired individuals almost invariably have multiple pathologies [2, 3]. Dementia with Lewy bodies (DLB), the second most common

neurodegenerative dementia, exemplifies this, with various co-pathologies being the norm rather than the exception [4–16]. However, the clinical impact of co-pathologies in DLB has been incompletely studied, as most studies are based on autopsy retrospective clinic-pathological correlation [9, 13, 14, 17–21]. In addition, some studies have not distinguished DLB and Parkinson's disease dementia participants, which, whilst representing different points along a Lewy body disease continuum, have differing clinical presentations and patho-aetiological mechanisms [7, 22].

DLB is clinically defined by the presence of dementia together with its core clinical features [5]: fluctuating cognition, well-formed recurrent visual hallucinations, REM behavioral sleep disorders, and parkinsonism. Research criteria now include the DLB prodromal stages for individuals with mild cognitive impairment, delirium-onset, and psychiatric-onset presentations [23]. These DLB clinical diagnostic and prodromal DLB research criteria also include indicative biomarkers tuned predominantly to impacts of α-synuclein-led neurodegeneration [5, 23]. Co-pathologies in DLB can impact clinical phenotype, disease progression, and structural and functional biomarker findings. Neurodegenerative co-pathologies are defined by the deposition of specific misfolded proteins [4, 24–33]. There are several biomarkers available to quantify Aβ and tau brain deposits *in-vivo*, thanks to the development of sensitive and specific biofluid and imaging biomarkers. In addition, several tissue and CSF assays are now available to detect α-synuclein presence [34–43]. Cerebrovascular pathology is the most prevalent non-neurodegenerative co-pathology with multiple manifestations that can be evaluated using MRI [2, 44, 45].

Evaluation of these co-pathologies may offer the opportunity to better predict clinical progression, enable individualized approaches to treatment, and improve the clinical trial design. Here, we evaluate the clinical features and presentation of DLB in the context of underlying co-pathologies and emerging biomarkers to their potential to quantify neuropathological change. We then consider the implications of these findings for future clinical trials.

Neuropathology and Prevalence of Co-Pathologies

DLB's hallmark is Lewy pathology, which encompasses Lewy bodies and Lewy neurites, defined by the presence of misfolded α-synuclein. Lewy pathology is also the hallmark lesion of Parkinson's disease (PD), and together both conditions are collectively classified as Lewy body disease. The DLB neuropathological criteria enable the evaluation of the likelihood of Lewy pathology leading to a DLB presentation [5]. However, the amygdala-predominant and brainstem stages do not lead to a DLB clinical presentation. DLB prevalence increases with age, but aging is also associated with an increased prevalence of multiple neurodegenerative and cerebrovascular diseases that contribute to cognitive impairment [2, 46]. Therefore, it is not surprising to observe multiple brain pathologies in aging individuals with cognitive and motor disorders [2, 3, 47]. In addition, neurodegenerative and cerebrovascular pathology have different distribution patterns and injury mechanisms, further adding to the heterogeneity of brain changes [44, 48–53]. The prevalence of these pathologies is outlined below and summarized in Table 1.

Alzheimer's Disease Pathology

Alzheimer's disease (AD) co-pathology, defined by the presence of amyloid-beta (Aβ) plaques and tau neurofibrillary tangles, is present in more than 50% of DLB individuals, with a higher prevalence compared to both Parkinson's disease (PD) and PD dementia (PDD) [6–10]. AD has been linked to a greater Lewy pathology burden [22, 51, 54] and is the only co-pathology considered when interpreting neuropathological findings in DLB that is recognized in the 2005 and 2017 guidelines [5, 55].

TDP-43 Pathology

Previous studies reported a wide prevalence range of TDP-43 pathology in DLB. Study differences are likely the result of differences in sampled areas and the definition of additional TDP-43 co-pathology. TDP-43 co-pathology in DLB follows an anatomical distribution consistent with limbic-predominant age-related TDP-43 encephalopathy (LATE) [12, 13, 27]. TDP-43 pathology burden is associated with greater Lewy pathology burden and the presence of AD co-pathology, exemplifying the complex interrelations between the different neuropathologies.

Frontotemporal Lobar Degeneration Tau and other Neurodegenerative Conditions

Frontotemporal lobar degeneration (FTLD) Tau pathology is less prevalent [22], and likely plays a minor role as a DLB co-pathology. Aging-related Tau astrogliopathy (ARTAG) is prevalent in individuals with dementia [56], including Lewy body disease (PD and DLB combined) [22].

Cerebrovascular Pathology

Cerebrovascular pathology inversely correlates with Lewy pathology [16] and DLB clinical features [57], which indicate that a lower threshold of neurodegenerative pathology may be necessary for clinical dementia expression in the presence of cerebrovascular co-pathology. Autopsy studies have reported a high prevalence of cerebral amyloid angiopathy (CAA) in up to two-thirds of individuals with DLB [13]. Increased CAA is more prevalent in DLB individuals with AD co-pathology. Within the Lewy body disease group, CAA is highest in DLB, followed by PDD, and lowest in cognitively unimpaired PD [13, 17]. Similarly, microbleeds are more frequent in DLB than in PDD, PD, and control participants [58–60]. In one neuroimaging study, microbleeds were associated with the systolic blood pressure but not with amyloid-beta (Aβ) PET values [61]. Compared to AD, DLB showed a similar burden of microbleeds [58]. There are inconsistent findings regarding the prevalence of infarcts in DLB compared to controls [16, 62], which might result from differences in the inclusion criteria of studies. A recent review showed no relationship between large cortical or small subcortical infarcts or intracerebral hemorrhage and the presence of Lewy body dementia [45]. Nevertheless, the same review showed increased MRI-assessed white matter hyperintensity (WMH) burden in individuals with DLB compared to cognitively unremarkable participants, which was consistently supported by neuropathological data. An ongoing challenge is that whilst WMH are considered a marker of cerebrovascular disease, other etiologies, including AD-associated pathology and axonal loss, may associate with WMH [63–65].

Clinical Impact of Co-pathologies in DLB

Co-pathologies are not only prevalent, but they will also likely affect the clinical presentation and disease progression by compounding brain dysfunction. Therefore, the impact of each co-pathology needs to be evaluated to predict clinical progression and understand the outcomes of treatments.

Cross-Sectional Clinical Associations of Co-Pathologies in DLB

From a cognitive standpoint, DLB individuals with an AD biomarker profile show poorer performance in memory and orientation tests than those without AD [72]. AD is the co-pathology with the greatest clinical impact, and pathological Aβ and tau levels have been related to worse global cognition [73–77]. Conversely, there are conflicting results regarding the effects of AD biomarkers values on the clinical presentation and core features of DLB. Several studies have reported that a higher burden of AD co-pathology or abnormally phosphorylated tau (p-tau) cerebrospinal fluid (CSF) levels decrease the odds of presenting core DLB features [9, 73, 78]. [79]. However, Aβ and tau PET studies have not found associations between AD biomarker positivity and DLB core features [74, 80, 81]. One study identified a higher frequency of visual hallucinations in DLB individuals with an AD CSF profile [82].

Limited data exist on the implications of TDP-43 co-pathology on clinical phenotype in DLB. One recent study found that individuals with TDP-43 co-pathology had a lower likelihood of presenting visual hallucinations and parkinsonism and were, therefore, less frequently diagnosed as probable DLB during life [15]. Although the presence of TDP-43 is also associated with older age and a higher likelihood of concomitant tau deposition, the lower likelihood of a clinical DLB diagnosis in individuals with Lewy pathology and TDP-43 co-pathology persisted even when considering these factors [15].

As noted above, cerebrovascular lesions in DLB correlate negatively with the severity of Lewy pathology [16, 83]. This association is consistent with cerebrovascular lesions lowering the threshold for dementia in individuals with AD and Lewy pathology [2]. However, the evaluation of WMH associations has led to conflicting results. WMH burden has shown inconsistent associations with visual hallucinations [57, 62], which may suggest that the location of the WMH makes a contribution [66, 84]. Several studies found no overall association of WMH with cognition [66, 69, 70, 84]. However, some studies point to the importance of WMH, which affect cholinergic white matter pathways and a modulating effect of apolipoprotein E (*APOE*) ε4 [57, 85, 86]. Parkinsonism and cognitive fluctuations are not associated with WMH burden [57]. The etiology of WMH in MR has also been debated and may reflect axonal degeneration due to cortical neuronal loss rather than ischemia/small vessel disease per se [65].

Limited information is available on the impact of ethnicity on DLB. One study reported a higher prevalence of Lewy pathology in African Americans than whites, although the study did not specifically evaluate DLB [87]. No results are available specifically considering co-pathologies. In a study assessing sex differences, AD co-pathology led to a lower frequency of RBD and parkinsonism in men and women, with men also presenting with

a lower frequency of cognitive fluctuations and visual hallucinations in the presence of AD co-pathology [88]. How the presence of co-pathologies impacts caregivers is unknown.

Longitudinal Associations of Co-Pathologies in DLB

DLB individuals with an AD CSF profile have a faster cognitive decline [89]. MMSE decline correlated with Aβ plaques, neurofibrillary tangles, and Lewy pathology [90]. The age of onset of dementia is lower in patients with high tau and amyloid beta [90, 91]. Overall, shorter survival appears to be linked with increased Aβ pathology [8, 92, 93], with a lower impact of tau pathology [8, 93]. The severity and distribution of Lewy pathology also have an effect; DLB patients with diffuse neocortical and occipital Lewy pathology showed a more rapid disease course than those with brainstem and limbic Lewy pathology [51, 93].

Implications of Genetic Findings

DLB shares its genetic risk factors with AD (*APOE*) [94–97] and PD (α-synuclein -*SNCA*- and β-glucocerebrosidase -*GBA*-) [96, 97]. However, different regions within *SNCA* have been associated with PD and DLB [96, 98], and *APOE* remains significantly associated with DLB in individuals with no or low burden of AD pathology [95]. Most of DLB's heritability is based on genetic risk variants associated with a small increase in DLB risk, with recent studies showing rare monogenic pathogenic mutations [99]. Clinically, *APOE* ε4 is associated with a faster disease progression and shorter survival in DLB [100, 101]. Future studies will need to evaluate the pathological changes that mediate this progression. Conversely, AD co-pathology is less prevalent in DLB individuals with *GBA* mutations [7]. These results indicate that genetic risk factors play an important role in the frequency of co-pathologies and clinical outcomes in DLB.

Biomarkers in the Setting of DLB Co-pathologies

An inherent limitation of the neuropathological studies is the cross-sectional evaluation of pathology at the time of death, which does not inform when these pathologies appear and how they interact during the disease's course. The recent explosion of available biomarkers has made it more possible to assess co-pathologies *in vivo*, enabling their detection even at prodromal disease stages. Biomarkers can be classified based on their modality or the pathological feature they quantify. From a modality perspective, biomarkers can be subdivided into neuroimaging, biofluid, neurophysiological, tissue-based (biopsy), and technology-based objective measures. Biomarkers can also be broadly divided into disease-specific and disease-nonspecific regarding the measured pathological feature. Disease-specific biomarkers include biomarkers that quantify specific changes to an underlying pathology, like Aβ biomarkers. Conversely, disease non-specific biomarkers measure changes that are not specific to a pathology, like brain atrophy evaluated using structural MRI sequences. We will discuss the utility of the biomarkers based on the pathological feature they measure because this aligns better with their role within a diagnostic and outcomes framework. These biomarkers are described below and summarized in Table 2.

Disease-Specific Biomarkers

Disease-specific biomarkers quantifying Aβ, tau, TDP-43, and α-synuclein are valuable biomarkers with the potential to indicate the presence of each co-pathology. Traditionally these biomarkers included CSF assays and PET scans [102–104], although, despite recent advances, there is still a lack of a sensitive and specific ligand for α-synuclein. Several studies show that PD individuals present lower CSF tau levels than controls [105–107]. It is unclear what is the reason for this phenomenon or whether this occurs in DLB. Further studies with autopsy validation will need to evaluate if different CSF tau biomarker cutpoints are needed in Lewy body disease, including DLB. Initial flortaucipir PET studies in DLB individuals indicate higher binding than healthy controls and cognitively unremarkable PD individuals, with a wide range of binding and correlate with MMSE scores [80, 108]. The newly developed plasma Aβ and tau assays will offer less invasive, easily deployable biomarkers [109–111]. Plasma tau levels are elevated in DLB individuals with pathological CSF Aβ values, and higher levels also predict worse baseline cognition and faster cognitive decline in the same individuals [110]. CSF real-time quaking-induced conversion (RT-QuIC) and protein misfolding cyclic amplification (PMCAand α-synuclein [42]assays can detect α-synuclein [43]. One manuscript presented a CSF TDP-43 RT-QuIC assay [112]. Initial studies in PD participants have shown high sensitivity and specificity of α-synuclein seeding assays, which have been tested in multiple tissues and biofluids with variable sensitivities [34–40], in addition to CSF. Some of these studies have also included DLB participants showing high accuracy in CSF and skin samples [36, 39]. In addition, skin α-synuclein immunohistochemical evaluation can accurately classify PD individuals [41].

Disease-Nonspecific Biomarkers

Disease-nonspecific biomarkers can measure synaptic loss, brain atrophy, neuronal dysfunction, and glial activation across different neurodegenerative diseases. These changes correlate with the degree of cognitive impairment in dementia and are known to play a significant role in disease presentation and progression [4, 113]. However, these biomarkers reflect changes secondary to a range of pathologies either in singular or in combination and must be interpreted accordingly in clinical practice and trials. These characteristics make these biomarkers suitable for investigating the underlying pathology's impact on DLB [4, 114].

Structural and Functional Imaging Biomarkers—Multiple structural and functional approaches have been evaluated in DLB [114], including MRI, CT, SPECT, EEG, and FDG-PET. As noted previously, biomarkers are now included in the diagnostic criteria for DLB [5] and, more recently, the research criteria for prodromal DLB criteria [23]. These neuroimaging modalities capture downstream, cumulative changes resulting from the combined pathologies present in DLB individuals (or any other dementia). The processed images can be scored using visual rating scales and easily performed in the routine clinical setting. Conversely, more quantitative measures like volumetry and cortical thickness quantifications are more sensitive techniques [115] and are desirable as outcome measures in clinical trials. They have been used to evaluate differences in brain atrophy patterns in people with DLB with and without underlying AD co-pathology [116, 117]. Neuroimaging implications of limbic TDP-43 co-pathology in DLB remain to be studied.

Changes in structural connectivity are evaluated using the diffusion tensor imaging (DTI) technique and higher tensor modeling techniques such as fixel-based analysis. These techniques have been applied in at-risk groups for PDD [118]; whether this approach is sensitive to tau and other co-pathologies within the DLB spectrum is still a topic of debate [119]. Emerging techniques sensitive to tissue changes, such as quantitative susceptibility mapping or quantitative multiparameter maps, have not yet been directly evaluated in DLB alongside pathological data but show greater promise based on correlations with clinical measures in PD [120]. Similarly, MRI substantia nigra free water values are increased in PD and atypical parkinsonism and could serve as diagnostic and imaging outcome measures [121, 122], but further work is needed in DLB.

Beyond structural changes, functional MRI and metabolic/perfusion nuclear medicine imaging techniques can track dysfunction in specific brain regions, including temporoparietal and occipital hypometabolism in DLB seen on 18F fluorodeoxyglucose (FDG) and SPECT perfusion imaging. The "cingulate island sign" (occipital hypometabolism with relative sparing of the posterior cingulate cortex) appears to distinguish those with DLB from other dementias [81]. It could indicate either nonsignificant or a low burden of AD co-pathology [123]. Different metabolic patterns have already been used to detect different underlying pathologies and progression risks in PD [124, 125]. However, their use is still limited in the DLB and needs further evaluation.

CSF and blood markers of neurodegeneration, synaptic dysfunction, and glial activation—Several non-specific neurodegenerative biomarkers have been developed to evaluate axonal damage, glial involvement, and synaptic dysfunction in CSF and blood samples.

Axonal damage can be quantified by measuring the neurofilament light chain (NfL), a structural component of the neural cytoskeleton. In axonal injury, NfL is released into the extracellular space leading to its increase in CSF and plasma [126, 127]. Higher CSF and blood NfL levels are already present in the prodromal DLB phase and correlate with short-term outcomes [127, 128]. The available evidence suggests that co-pathologies influence NfL because its values increase across multiple types of brain injuries, including neurodegenerative, traumatic, inflammatory, and vascular conditions [127, 129]. Glial-related markers are elevated in DLB compared to controls [130]. Proposed biofluid biomarkers of synaptic dysfunction have not yet been assessed in DLB [113].

Integration of Multiple Biomarkers—Traditionally, a single diagnosis has been assigned to patients with motor or cognitive disorders. Following this approach, biomarker studies aim to distinguish one pathology from the other, assuming they are mutually exclusive (Figure 1A). However, neuropathological studies have demonstrated that cognitively impaired individuals have multiple pathologies leading to their cognitive changes [46, 47]. The AT(N) framework accommodates the integration of different processes (Aβ, tau, and neurodegeneration) to classify individuals within the AD spectrum [131, 132]. The latest version of the AT(N) framework also discusses the possibility of categorizing biomarker values into a three-range approach and evaluating biomarkers targeting other pathologies to assess their potential contribution in AD. We propose a new biomarker

quantitative approach (Figure 1B) in DLB that integrates pathology disease burden (Aβ, tau -differentiating different tau species-, TDP-43, and vascular changes) and processes such as inflammation and neurodegeneration into different quantitative axes leading to a specific biomarker fingerprint for each individual. It also includes normal and pathological range definitions. The integration of quantitative values in the fingerprint allows for potential changes in biomarker cutpoints (red and green shading boundary) on an individual basis based on established factors that impact biomarker performance (adjusting plasma biomarker cutpoint values based on renal clearance, or gray matter volume/thickness cutpoints based on age).

Implications for Clinical Trial Design

The new diagnostic criteria and the increasing number of Lewy pathology biomarkers will facilitate the recruitment into clinical trials by including participants at potential earlier stages and greater access to biomarkers to increase the diagnostic sensitivity and exclude participants without Lewy pathology.

Most clinical trials have not evaluated the impact of co-pathologies on treatment response. Evaluating co-pathologies in future clinical trials will be crucial because of their impact on clinical presentation, cognitive performance, disease progression, and biomarkers, as summarized above [6, 7, 73–77, 82, 89, 152, 153]. One study suggested that treatment with acetylcholinesterase inhibitors (AChEI) was associated with a slower rate of cognitive decline in DLB patients with concomitant AD (although, in this study, DLB without AD were not evaluated) [154]. Conversely, DLB individuals with negative amyloid PET scans experience a more significant response to AChEI treatment than those with positive Aβ PET scans [155].

There are two overall consequences of co-pathologies for DLB clinical trial design. First, co-pathologies in DLB will need to be treated, for example, the administration of AD disease-modifying therapies (and symptomatic therapies) in DLB participants with AD co-pathology. Second, clinical trials evaluating DLB-specific treatments should stratify DLB participants and account for the potential effect of co-pathologies. This approach will be relevant for symptomatic therapies or treatments that do not specifically target Lewy pathology. However, in clinical trials targeting Lewy pathology (or another disease-defining protein deposit), participants could be selected based on their biomarker-defined presence instead of the clinical presentation.

In theory, participants with DLB with coincident AD pathology or vascular risk factors may benefit from disease-modifying therapies that successfully treat these conditions. This approach could also be extended to symptomatic therapies. To test this hypothesis, successful disease-modifying therapies and symptomatic treatments for co-pathologies should be evaluated in randomized clinical trials recruiting DLB individuals with co-pathologies confirmed by appropriate disease-specific biomarkers.

Current neurodegenerative disease clinical trials confirm the presence of the targeted pathology using biomarkers, but these trials usually do not account for the presence of

co-pathologies. Therefore, clinical trials design calls for a combination of biomarkers to confirm the pathology of interest and to identify relevant co-pathologies. This information would have multiple applications: 1) influencing the inclusion and exclusion criteria for study entry, 2) trial stratification and evaluation of outcomes during the clinical trial, which includes integration of a multi-modal biomarker approach that is able to model the impact of each co-pathology. Biomarker use could decrease participant heterogeneity to increase effect sizes and decrease sample sizes, but current evidence in DLB is insufficient to evaluate the potential benefits.

These disease-specific biomarkers identify the misfolded proteins that define the different neurodegenerative conditions and therefore detect the different co-pathologies. However, these same biomarkers might not be adequate clinical trial outcome measures, at least based on recent AD clinical trials targeting Aβ [156, 157]. Therefore, disease non-specific biomarkers that define downstream changes closer to the cognitive outcomes could represent better outcome measures [131, 156, 157]. Future prospective cohort studies need to investigate how quantifying these co-pathologies informs longitudinal clinical changes and neurodegeneration biomarkers that could serve as outcomes in clinical trials [158].

There is insufficient data from clinical cohorts characterizing biomarkers performance, genetic heterogeneity, and co-pathology prevalence in DLB individuals with multiple comorbidities or belonging to different minority and underserved populations leading to health disparity. This lack of diversity and access difficulty in research studies and clinical trials is not unique to DLB [159]. In addition, stringent clinical criteria and lack of diverse recruitment in clinical trials also can limit the generalizability of their results and an equitable access to them as highlighted in other medical fields [160]. Studies including AD participants have shown differences in biomarker values in these groups [158, 161]. Ongoing and upcoming DLB clinical studies and trials need to consider the multiple aspects laid out by the National Institute on Aging Health Disparities Research Framework [162]. Strategies to increase enrollment and access to research studies and clinical trials are vital to achieving these goals [163]. In the future, plasma biomarkers could offer a less invasive and more cost-effective diagnosis. Disease-specific plasma biomarkers are at a more advanced stage in AD; however, they are currently not ready to be used as a stand-alone diagnostic marker o in primary care [164].

Figure 2 summarizes a framework to evaluate and account for co-pathologies in DLB clinical trials. It aims to integrate multi-modal biomarker approaches in DLB to develop personalized treatment selection and outcome evaluation approaches. The first stage includes the selection of the disease stage and phenotype based on clinical criteria. Earlier disease stages, including prodromal DLB [23] and rapid eye movement behavioral disorder (RBD) [165], offer earlier treatment windows. The second step includes DLB biomarkers to confirm the underlying Lewy pathology. The third step would consist of biomarkers that assess the presence of co-pathologies and quantify neurodegeneration. All this information is integrated during the fourth step to identify subgroups and different progression rates for endophenotyping and stratification. This leads to personalized treatment selection in step 5. Step 6 evaluates target engagement biomarkers that track changes that correlate with future clinical outcomes.

This framework can also accommodate innovative clinical trial designs such as adaptive methodologies and master protocols [166]. Adaptive methodologies are pre-specified modifications to a clinical trial protocol during the data collection period [167], which include: changes to eligibility criteria, endpoints, dosage or patient allocation, sample size re-estimation, and addition or termination of treatment arms [168]. These modifications can be implemented in master protocols, a type of clinical trial that uses a single protocol to test a single drug in different diseases (basket trial), multiple drugs in a single disease (umbrella trials), or multiple therapies (separately or in combination) in multiple diseases in parallel (platform trials) [169]. These novel designs improve operational efficacy, include broader patient populations, share a single common control group (thus requiring fewer participants), cycle between therapies, simplify comparison across sub-studies, and increase the number of treatments tested [169]. These new methodologies could improve our ability to account for co-pathologies.

Conclusion

Individuals with DLB frequently present concurrent co-pathologies that impact clinical presentation and progression. Therefore, it is likely that combined disease-specific disease-modifying therapies will be required to affect all the pathologies contributing to the clinical signs and symptoms. However, our current understanding of co-pathologies' impact is limited because current evidence is mainly derived from retrospective autopsy studies. Another challenge is identifying ideal disease non-specific biomarkers that closely correlate with clinical outcomes and serve as reliable clinical outcomes. An additional caveat is that these disease non-specific biomarkers pathologies might reflect changes from multiple pathologies.

Future approaches will require integrated multi-modal biomarkers with different functions. To inform clinical trials and care, we need cohort studies that evaluate disease-specific biomarkers to characterize the prevalence, impact, and progression of co-pathologies in prodromal and early dementia stages. Clinical trials will also need disease-nonspecific biomarkers that closely correlate with meaningful clinical outcomes and serve as outcomes in clinical trials. The design of these cohort studies should further evaluate the studied biomarkers' current evidence to advance them towards clinical application and provide initial evidence of the emerging biomarkers [170]. The cohorts should recruit DLB individuals representing diverse socioeconomic, races, ethnicities, and risk factors.

Here, we proposed a multi-axial biomarker integration approach and a multi-step process for selection, stratification, evaluation of target engagement, and interpretation of clinical trial results in DLB. This multi-layered biomarker approach will provide a personalized assessment of pathologies guiding recruitment into clinical trials and interpreting its outcomes. Once disease-modifying therapies are available, this process will help predict different response rates to treatments and guide potential treatment approaches that combine various drugs targeting each pathology present in the brain.

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Acknowledgments

Conflicts of interest

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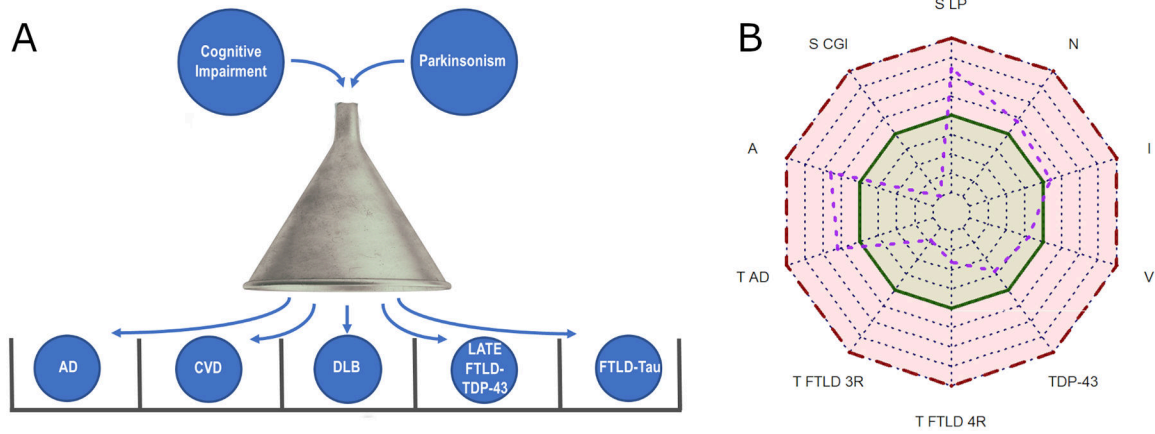
Figure 1. Application of diagnostic biomarkers.

A) Biomarker applied to identify a single pathology/diagnosis and exclude other pathologies/diagnoses (differential exclusion diagnosis). B) Application of biomarkers to independently identify the different underlying processes leading to cognitive and movement disorders. The radar chart approach accommodates the inclusion of quantitative biomarker data along each axis, including a threshold into normal (green) and pathological (red) biomarker value ranges and offering a specific biomarker fingerprint for each individual. The purple line and dots represent a hypothetical patient. A: Amyloid β; AD: Alzheimer's disease; CGI: Cytoplasmatic glia inclusion; CVD: Cerebrovascular disease; DLB: Dementia with Lewy bodies; FTLD: Frontotemporal lobar degeneration; I: Inflammation; LATE: Limbic-predominant age-related TDP-43 encephalopathy; LP: Lewy pathology; N: Neurodegeneration; S: α-Synuclein; T: Tau; S: α-synuclein; V: Cerebrovascular pathology; 3R: 3-repeat tauopathy; 4R: 4-repeat tauopathy.
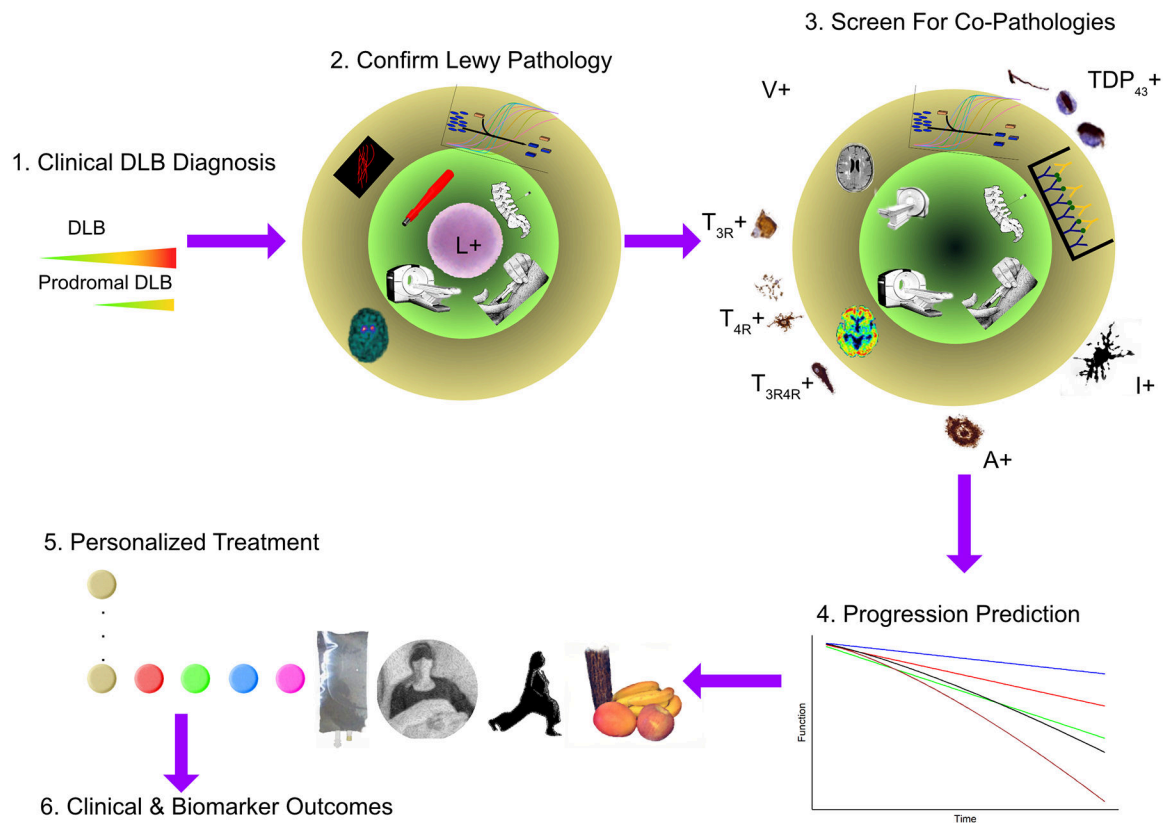
Figure 2. DLB clinical trial framework accounting for the presence of co-pathologies.
After the initial selection of participants based on clinical disease severity (step 1), Lewy pathology needs to be confirmed based on α-synuclein disease-specific biomarkers (step 2). Co-pathologies are then screened using additional biomarkers (step 3). The combined biomarker information could be part of exclusion or inclusion criteria or be considered during the clinical trial for stratification (step 4) or as co-variates. The biomarker fingerprint (See figure 1B) will estimate the predicted disease progression rate and identify the combination of treatments for each individual (step 5). Finally, biomarkers can be used to verify target engagement and as clinical trial outcome measures (step 6). In steps 2 and 3, the inner green circle represents the biomarker modalities like skin biopsies, neuroimaging (PET, SPECT, and MRI), blood, and cerebrospinal fluid). The outer circle represents the biomarker measurement, including radiotracer binding, quantification of vascular pathology through MRI, immuno-assays, real-time quaking-induced conversion, or protein misfolding cyclic amplification performed on biofluid samples.

Table 1

Co-pathology in dementia with Lewy bodies

Type of Neurodegenerative Condition	Type of Pathology	Prevalence in DLB
Alzheimer's disease	Amyloid-beta (Aβ) plaques Tau neurofibrillary tangles	48–88% of individuals with DLB have intermediate- or high-level AD pathology versus 17–62% in PDD and 7–10% in those with PD who are dementia free [7–10]. AD pathology is associated with a greater Lewy pathology burden [51].
TDP-43 and limbic-predominant age-related TDP-43 encephalopathy (LATE)	TDP-43	13–60% of individuals with DLB [11–15] More prevalent in the advanced neocortical Lewy pathology (LP) stages, in the presence of AD co-pathology in DLB vs. individuals with PD who are dementia-free [11, 13, 15]
Frontotemporal lobar degenerations Tau (FTLD)	Tau	Less prevalent compared to other co-pathologies
Other Tau-related neurodegenerative conditions, including aging-related Tau astrogliopathy (ARTAG)	Tau	Not studied in DLB alone In Lewy body disease overall (PD + DLB): 31% of participants without AD co-pathology [22] 72% in the presence of AD co-pathology [22]
Cerebrovascular Pathology	Microinfarcts Gross infarcts	**Neuropathological samples** [16] Microinfarcts 26.7% Gross infarcts 6.7%[16] **MRI-based samples]** [57, 62] 18.8–27%
	Cerebral amyloid angiopathy (CAA)	**Neuropathological samples** CAA 66.7% none to intermediate AD neuropathological changes versus 94.7% CAA prevalence in individuals with high AD neuropathological changes [13] CAA is highest in DLB (82%–91%), followed by PDD (50%), and lowest in cognitively unimpaired PD (21.7%) [13, 17]
	Cerebral microbleeds (usually associated with CAA)	Are also more frequent in DLB (30%–45.2%) than in PDD (26.1%), PD (11.5%), and control participants (17.1%) [58–60]. However, one study that compared participants with DLB with and without microbleeds did not find differences in florbetapir binding and found that high systolic blood pressure was the factor associated with microbleeds in DLB [61]
	White matter hyperintensities (WMH) burden	It may be ↑ in DLB vs. healthy controls [59, 62, 66–68], although reports are inconsistent [69–71]

Table 2:

Biomarkers in the Setting of DLB Co-Pathologies

Pathological change	Biomarker modality	Implications in dementia with Lewy bodies
Disease-Specific Biomarkers		
Aβ	CSF and PET biomarkers Plasma assay [109]	Both modalities accurately predict the presence of Aβ plaques in the brain [102, 133] and are in good agreement with each other [103]. Conversion to pathological values of CSF Aβ tends to precede PET abnormalities [134].
Tau	CSF and PET biomarkers Plasma assay [110]	Correlates with tau brain deposition [102, 135]; typically detect neurofibrillary tangle pathology present in AD rather than FTLD-Tau pathology [136, 137]. New tracers are being developed to quantify FTLD-Tau pathology [138].
α-synuclein	CSF real-time quaking-induced conversion (RT-QuIC) [39, 42] and protein misfolding cyclic amplification (PMCA) [43] Skin [34–36, 39, 41] Olfactory Mucosa [37–39] Submandibular gland [39, 40] Colon [39]	Binary detection of the presence/absence of α-synuclein only. Less useful to quantify disease progression. Further studies are needed in DLB.
Disease Nonspecific Biomarkers		
Synaptic loss	CSF and blood biomarkers [113]	Structural and functional imaging alterations are strongly correlated with fluid-based biomarkers of synaptic and neurodegenerative tissue change [139].
Brain atrophy	Imaging techniques using either MRI	Correlates with the degree of cognitive impairment and is known to play a significant role in disease presentation and progression [114]. Present in brain aging and can follow a different pattern in cognitively impaired individuals [140, 141].
Neuronal dysfunction and damage	CSF and blood biomarkers [128, 142]	Structural and functional imaging alterations strongly correlate with fluid-based biomarkers of synaptic and neurodegenerative tissue change [139] and can track change *in-vivo* [113].
Glial activation	CSF and blood biomarkers [130]	
Structural and Functional Imaging Biomarkers		
Relative preservation of medial temporal lobe structures	MRI CT	Included in the diagnostic criteria for DLB [5].
Reduced basal ganglia dopamine transporter uptake	SPECT	
Increased focal and diffuse abnormalities	EEG	
Reduced occipital metabolism/cingulate island sign	FDG-PET	
Insular thinning and gray matter atrophy	MRI	Reported as requiring further investigation in the research criteria for prodromal DLB.
Medial temporal lobe structures atrophy	Visual rating scales	Greater atrophy in multiple brain regions than in controls and relative preservation of medial temporal lobe structures compared to AD [143–145]. AD co-pathology is associated with greater medial temporal lobe atrophy in DLB, demonstrating that AD co-pathology (and possibly TDP-43) modifies imaging patterns in people with DLB [143, 146, 147].
Abnormalities in the cholinergic system	Volumetry and cortical thickness quantifications	Atrophy of nucleus basalis of Meynert in prodromal MCI stages [148] Associations between nucleus basalis of Meyner atrophy, Aβ, and cognitive changes differ in AD and DLB [149].

Pathological change	Biomarker modality	Implications in dementia with Lewy bodies
Limbic TDP-43 co-pathology	RT-QuIC [42]	Studies are needed in DLB.
Higher WMH burden	MRI	Associated with more neurodegeneration in DLB [57, 67, 150], particularly in brain areas that receive dense cholinergic input [57], which may have implications for the cholinergic treatment of DLB.
Structural connectivity changes	Diffusion tensor imaging (DTI) technique and higher tensor modeling techniques such as fixel-based analysis	Seen in at-risk groups for PDD [118]. Studies are needed in DLB.
	Quantitative susceptibility mapping Quantitative multiparameter maps	Applied in PD [120], revealing a correlation with clinical change. Studies are needed in DLB.
Temporoparietal and occipital hypometabolism	18-Fluorine 18F fluorodeoxyglucose (FDG) and SPECT perfusion imaging	Further studies are needed in DLB with co-pathologies.
"Cingulate island sign"	FDG-PET	May indicate a lower Braak neurofibrillary tangle stage at autopsy [123].
Abnormalities in serotonergic systems	Volumetric measures and PET radiotracers	Further studies are needed in DLB with co-pathologies.
CSF and blood markers of neurodegeneration, synaptic dysfunction, and glial activation		
Neuro-axonal damage	Neurofilament Light (NfL)	Elevated already in prodromal DLB stages, higher levels in the presence of AD co-pathology [151].
Glial-related change	Glial fibrillary acidic protein (GFAP), the soluble triggering receptor expressed on myeloid cells 2 (sTREM2, mainly expressed by microglia), and S100 calcium-binding protein B (S100B, mainly expressed by astrocytes).	Elevated in DLB compared to controls [130].
Synaptic dysfunction	Fluid-based biomarkers: synaptosomal-associated protein 25 (SNAP-25), Synaptogamin-1, neurogranin, and β-synuclein.	Further studies are needed in DLB with co-pathologies.

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