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PERSPECTIVE

Listening session with the US Food and Drug Administration, Lewy Body Dementia Association, and an expert panel

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Abstract

The regulatory path for drug approval is increasingly well defined. Drugs for the treatment of Alzheimer disease (AD) need to show statistically significant benefit over placebo with respect to cognitive and functional measures, with the Clinical Dementia Rating scale and Alzheimer's Disease Assessment Scale–Cognitive Subscale being among the most often used instruments in AD clinical trials. In contrast, there are no validated instruments for use in clinical trials of drugs for the treatment of dementia with Lewy bodies. This poses challenges for drug development because the regulatory pathway to drug approval requires demonstrable efficacy measures. In December 2021, the Lewy Body Dementia Association advisory group met with representatives from the US Food and Drug Administration to discuss the lack of approved drugs and treatments, discernment of efficacy measures, and identification of biomarkers.

KEYWORDS
clinical trials, dementia with Lewy bodies, drug development, outcome measures, regulatory pathways

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Highlights

- The Lewy Body with Dementia Association convened a listening session with the US Food and Drug Administration on dementia with Lewy bodies (DLB) and clinical trial design.
- Gaps include DLB-specific measures, alpha synuclein biomarkers, and coexisting pathologies.
- DLB clinical trial design should focus on clinical value and disease specificity.

1 | INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most common type of dementia after Alzheimer's disease (AD) and accounts for 10% to 12% of neurodegenerative dementia.[1] DLB is among those dementias caused by synucleinopathies,[2] a category that includes both DLB and Parkinson's disease dementia (PDD), collectively known as Lewy body dementia (LBD). Differentiating DLB and PDD can be challenging, but current clinical criteria define PDD as occurring in individuals for whom the movement disorder begins first, at least 1 year before dementia; up to one third of people with Parkinson's disease (PD) may have mild cognitive impairment at the time of PD diagnosis. DLB is characterized by early cognitive impairment with or without motor parkinsonism. Although LBD includes both PDD and DLB, this report focuses on DLB.

DLB is more common among men and is associated with a faster decline than AD.[3] It is estimated that there are 1.4 million persons living with LBD in the United States. Prevalence estimates of DLB range from 0% to 5% in the general population and from 0% to 30.5% among all dementia cases.[4,5] Incidence rates of 0.1% in the general population and 3% among all new dementia cases have been reported. A recent review that examined 22 studies reported incidence rates between 0.5 cases and 1.6 cases per 1000 person-years, accounting for 3% to 7% of dementia cases.[6] Prevalence estimates ranged from 0.02 cases to 63.5 cases per 1000 person-years and were higher with increasing age.[6] Direct costs for patients with DLB in the United States are approximately twice those of patients with AD at $31.5 billion per year.[5] DLB is now estimated to be the most expensive dementia.[7] Estimates suggest that the number of people with DLB could increase from 5.5 million to 14 million worldwide by 2050.[8] DLB causes significantly greater functional disability than AD.[9] Care costs for DLB are twice those for AD.[10] The quality of life is significantly worse for people with DLB than for those with AD, with 25% of caregivers rating DLB as "worse than death."[10]

There are many challenges associated with DLB, ranging from accurate and timely diagnosis to effective and safe therapeutics. Despite recognition of the condition and clinical criteria that are highly specific in predicting neocortical alpha-synuclein–positive Lewy body pathology, there is often a significant delay in diagnosis because of a lack of recognition by treating physicians and a delay in implementing treatments for symptoms because of a lack of approved treatments for the myriad DLB features. A correct diagnosis increases the chances of correct management.[11] Critically, the available drugs address only the symptoms of the disease, and many are not specifically approved for DLB, may have significant adverse effects, and may require balancing treatment of motor and cognitive symptoms.

Identifying cases of probable or possible DLB relies on clinical criteria. Diagnosis requires the presence of progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuo-perceptual ability may be especially prominent and may occur early. Core clinical features include fluctuating cognition, with pronounced variation in attention and alertness; recurrent visual hallucinations that are typically well formed and detailed; rapid eye movement (REM) sleep behavior disorder, which may precede cognitive decline; and one or more spontaneous cardinal features of parkinsonism: bradykinesia, rest tremor, or rigidity. Supporting clinical features include severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; insomnia; severe autonomic dysfunction (e.g., constipation, orthostatic hypotension, and urinary incontinence); hallucinations in other modalities; systematized delusions; and apathy, anxiety, and depression.[12]

Symptoms associated with DLB and relatable to neuropathology include motor symptoms (slowness, stiffness, imbalance and falls, tremor, shuffling gait, and myoclonus); behavioral symptoms (visual hallucinations; other hallucinations; delusions; depression, anxiety, and apathy; REM sleep behavior disorder; and cognitive fluctuations); cognitive symptoms (visual tracking and attention, visual perception, verbal initiation, timed attention, executive tasks, slowed thinking, and slowed processing speed); and constitutional symptoms (loss of smell, constipation, urinary incontinence, drooling, rhinorrhea, dizziness, lightheadedness, fainting, abnormal sweating, and sexual dysfunction). Although most of the clinical criteria lack sensitivity, they are highly specific and strongly correlated with pathology.

There are many gaps that hinder clinical trials and the development of drugs for DLB treatment. A critical gap is the lack of disease-specific biomarkers. Currently, biomarkers are used in clinical

practice and research. Indicative biomarkers outlined in the DLB criteria include reduced dopamine transporter uptake in basal ganglia by positron emission tomography (PET) or single-photon emission computed tomography (SPECT); abnormal (low) uptake meta-iodobenzylguanidine myocardial scintigraphy; and polysomnographic confirmation of REM sleep without atonia. Supportive biomarkers include relative preservation of medial temporal lobe structures on magnetic resonance imaging or computed tomography, generalized low uptake on SPECT or PET with reduced occipital activity with or without cingulate island sign on 18F-fluorodeoxyglucose PET, and prominent posterior slow wave activity on electroencephalography. The biomarkers, however, are only proxy measures and are not direct measures of alpha-synuclein protein or Lewy bodies. Ideally, cerebrospinal fluid, plasma, skin, or imaging biomarkers of these protein aggregates could fill the gap, and seed amplification assays, which are under advanced development, can help with this need.

A major gap is the absence of approved drugs to treat DLB. This is a large unmet need for millions of people living with DLB. Drugs that are used off-label in the United States include cholinesterase inhibitors and memantine for cognitive symptoms; dopaminergic medications for motor symptoms; modafinil and armodafinil for cognitive fluctuations and attention; antidepressants, atypical antipsychotics, antiepileptics, and prazosin for behavioral symptoms; melatonin and clonazepam for sleep disturbance; and fludrocortisone, midodrine, droxidopa, and trospium for autonomic dysfunction.[13–15] In Japan, donepezil is approved to treat DLB. In the United States and Europe, rivastigmine is approved to treat PDD, which has many characteristics in common with DLB.

With respect to translational studies, industry and academic investigators should be engaged to conduct more clinical trials and to define valid and accepted clinical trial outcome measures.[16] Although rivastigmine is approved to treat PDD in the United States, there have been relatively few studies on it specifically directed at DLB. Trials to date have included HEADWAY-DLB (which assessed intepirdine),[17] PRESENCE (which assessed mevidalen),[18] and AscenD-LB (which assessed neflamapimod).[19] All three DLB studies included cognitive and motor symptoms, but inclusion and exclusion criteria differed among the studies, with some including participants with PDD. The intervention durations ranged from 12 to 24 weeks but were not uniform. Primary outcome measures were mainly focused on cognitive measures, such as the Alzheimer's Disease Assessment Scale, and global measures, such as the Clinical Dementia Rating (CDR) scale and the Clinical Global Impression of Change scale. Mevidalen was associated with improvement of motor symptoms as measured by the Unified Parkinson's Disease Rating Scale, and neflamapimod was associated with improved performance on the CDR–Sum of Boxes and the Timed Up and Go Test compared to placebo.[19] Most studies did not report statistically significant results favoring treatment for their respective primary cognitive endpoints. One lesson from the previously conducted studies is the importance of successful identification of the study population and study operationalization. It is possible to recruit and retain people with DLB into clinical trials of varying durations. Furthermore, it is possible to conduct DLB clinical trials that have a reasonable study burden and well-defined inclusion–exclusion criteria. This is promising for the field and for the development of drugs to treat DLB. However, biomarker confirmation and medication standardization are lacking in these trials. In addition, outcome measures that are specific and sensitive to DLB are also lacking. Until now, AD-specific measures, such as the Alzheimer's Disease Assessment Scale–Cognitive Subscale, have been used in DLB trials, but that measure is not sensitive to changes over a 4- to 6-month period, which would be more appropriate to evaluating individuals with DLB. Global measures and patient-reported outcomes (PROs) may be more sensitive than AD-specific measures. Thus, DLB-tailored cognitive measures (e.g., CDR and Neuropsychological Test Battery used in the neflamapimod trial) are needed; their development may be feasible, but this area is not yet fully studied.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors searched PubMed for references to synthesize their perspective in view of the published Alzheimer.s disease (AD) literature.
2. **Interpretation**: Traditional clinical trial measures used in AD clinical trials should be reconsidered in the context of dementia with Lewy bodies (DLB). The Clinical Dementia Rating Scale should be reviewed, revised, and validated for DLB. Alternative outcome measures can be developed that detect and quantify unique features of DLB including hallucinations, parkinsonism, REM sleep behavior disorder, and fluctuations. These measures should consider analytical methodologies.
3. **Future Directions**: Alternatives or adaptations of the existing clinical trial outcome measures for DLB require validation. Does it make sense to require clinical and functional efficacy measures? Could composite measures that include function and cognition be merged into single endpoints that could be validated? Alternative analytical methods should be discussed and explored. Disease-specific biomarkers should be evaluated and validated as outcome measures.

1.1 | Purpose of the meeting with the US Food and Drug Administration

With industry-sponsored clinical trials becoming increasingly common, the Lewy Body Dementia Association Research Centers of Excellence program is poised to contribute recommendations to clinical trial designs that lead to approvable drugs. The purpose of the meeting, which was called a listening session, with the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) was to inform the FDA CDER of the opportunities and barriers associated with DLB clinical trials and to prepare a consensus statement to

inform the field regarding progress in and problems with DLB clinical trial design. The panel of physician–scientists in attendance sought to provide the FDA with input on considerations related to the evidence of efficacy of drugs developed for DLB that could support regulatory approval.

The meeting was held virtually via a Zoom call on December 9, 2021. The FDA began the meeting with prepared statements, confirming that this meeting was a listening session and not a regulatory meeting. In this type of session, any feedback from the FDA is non-binding and should not be construed or interpreted as policy. The meeting was intended to inform the FDA about the disease; disease information will be shared with other key stakeholders at the FDA. Attendees included the authors, representatives of the Lewy Body Dementia Association, National Institutes of Health program officers, and representatives of the FDA CDER. The topics discussed at the meeting included primary outcome measures and patient selection. Patient consent was not required for this report, which involved no human subjects.

2 | DISCUSSION

2.1 | Primary outcome measures

The meeting provided confidence that the FDA has appreciation for the considerable heterogeneity of the symptoms of DLB and the paucity of data currently available to guide selection of outcome measures for drug development. Recent industry-sponsored trials in the DLB population, which relied on existing measures drawn from AD, underscore this reality.

Because the DLB clinical profile differs significantly from that of AD, DLB trial design cannot necessarily use an "AD plus" approach. For example, memory loss is not as common among individuals with early DLB; therefore, memory-predominant AD instruments would be less useful in DLB trials. The CDR, which has been widely used in AD trials, has been used in DLB trials as well because it is broad and covers many domains.

The paucity of data and the lack of a "gold standard" instrument should not be barriers to designing DLB trials, and we cannot wait until better measures are developed to design such trials. Incremental learning related to study design and measures is to be expected, and existing scales developed for other diseases should be used if there is an expectation that the tool will accurately measure change in DLB.

There are strong rationales for using scales that may demonstrate clinically meaningful change to the participant but have not yet been validated in DLB. Validation of new or existing measures for this complex, progressive disease will be complicated. Regardless of the measure used, demonstrating an effect on function and on what is clinically meaningful to patients is key for marketing applications and improving the lives of people affected by DLB.

Evidence should confirm that the therapy affects one aspect or symptom of a disease or a subset of the disease. As disease knowledge evolves, the mechanistic specificity of treatment should be taken into consideration because it can influence the context in which the FDA evaluates trial results.

Although AD trials have historically used both cognitive and global primary endpoints, the field is evolving. More recent trials use measures with endpoints that are more encompassing of symptoms and function, such as the CDR–Sum of Boxes, which allows improvement in memory, for example, to be assessed in a more meaningful way than with neuropsychological tests and better reflects everyday aspects of living with the disease. Novel thinking is needed to craft appropriate endpoints for DLB measures. A global endpoint may need to be very comprehensive to address the wide array of DLB symptoms, which include cognitive, motor, behavioral, and autonomic symptoms and cognitive fluctuations. Such a global endpoint is key for trials of disease-modifying therapies. As in other disease states, endpoints for symptomatic treatments might be different from endpoints for disease-modifying therapies. Disease-modifying therapies typically target the trajectory of decline as primary measures, which might be difficult to determine in DLB. However, fluctuations in clinical characteristics such as cognition and arousal are left unaddressed. Specifically, such fluctuations might confound the interpretation of therapeutic effects and should be addressed in trial design.

For symptomatic therapies, endpoints would vary to focus more directly on the target symptom (e.g., motor, behavioral, sleep-related, or autonomic symptoms). More work is needed to develop scales for DLB that encompass these different domains and to optimally integrate these scales into clinical trials.

The use of PROs to capture how the symptoms affect function in daily life directly from the patient's perspective is encouraged. However, patients may lack insight into their problems. Therefore, informant questionnaires and physician assessments may be needed to supplement PROs. Clinician-rated activities of daily living scales may not be as useful because function can be affected by illness or other factors not related to the study drug. Therefore, PROs and clinician-related scales might be complementary to different aspects of the disease and patient or caregiver condition. Interpretation of PROs and clinician-related scales might be confounded by cognitive fluctuations, concomitant medications, rate of progression, and disease severity. PROs would ideally be used in assessing treatment outcomes for neurodegenerative diseases such as AD and DLB, but to date they have not been accepted as primary outcome measures.

2.2 | Patient selection

The study design may include multi-arm trials with separate arms for DLB and PDD participants to identify similarities or differences between these LBD populations. In addition, trials should be adequately powered to provide statistically valid findings to compare the treatment group against the control or placebo group, whether the trial is assessing DLB and PDD separately or in combination.

If issues that add complexity to DLB trials, like fluctuating cognition, can be prospectively identified, they can be studied in a protocol. Careful consideration of the methodology for statistical adjustment

of longitudinally collected cognitive and other assessments can be an element of future regulatory discussions.

Gaps include the need for the field to address the potential trial confounder of mixed disease pathologies in both AD and DLB clinical trials. Indeed, at least 50% of autopsy-confirmed AD cases are associated with a significant alpha-synuclein LBD co-pathology, and ≈70% to 80% of autopsy-confirmed DLB cases are associated with clinically significant AD co-pathology in most large-scale autopsy studies. If research reveals different clinical responses to treatment based on single versus mixed pathophysiologies, the DLB consensus criteria may need to be revisited to incorporate this finding. Inviting the FDA to participate in consensus-building workshops is encouraged to address implications for clinical trials.

The ability to diagnose DLB biologically is critical for enrolling presymptomatic and mildly symptomatic patients in trials of potential disease-modifying therapies. The increase in clinical trials of disease-modifying therapies for AD may lead to revisiting the clinical diagnostic criteria for other neurodegenerative dementias to incorporate prodromal symptomatology and biological diagnosis of DLB.[20]

A better characterization of the disease biology and its correlation with the clinical course is also needed. Understanding the clinical expression of DLB will remain important, but the field is moving toward earlier diagnosis, including the incorporation of biomarkers of underlying disease-specific pathology in early diagnosis (Supporting).

3 | CONCLUSIONS

The Lewy Body Dementia Association convened an advisory committee of physician–scientists to meet with representatives of the FDA CDER on the topic of DLB and clinical trial design. Gaps identified included the need for DLB-specific measures, direct biomarkers for alpha synuclein pathology, and strategies to address coexisting pathologies. A dual focus on clinical meaningfulness and disease specificity should be considered in DLB clinical trial design because clinical meaningfulness is often discussed as it pertains to translating clinical trial outcomes to clinical care and effect on patients and caregivers.

The next steps to be taken to address these issues might include support of developing clinical trial designs and outcome measures that are validated in longitudinal cohorts, like the cohorts followed-up as part of the Dementia with Lewy Bodies Consortium. Other steps might include pilot studies of novel trial designs and outcomes in a therapeutic trial. It will take time and investment to identify druggable outcome measures that can render prima facie evidence of efficacy in DLB.

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CONFLICTS OF INTEREST STATEMENT

Dr. Sabbagh has ownership interest (stock or stock options) in NeuroTau, uMethod Health, Athira, TransDermix, Seq BioMarque, NeuroReserve, and Cortexyme/Quince Therapeutics and is a consultant for Alzheon, Roche-Genentech, Eisai, KeifeRx, Lilly, Synaptogenix, NeuroTherapia, T3D, Signant Health, and Novo Nordisk. Dr. Sabbagh also receives royalties from Humanix and is on the Board of Directors for EIP Pharma. No other authors have any personal, financial, or institutional interest in any of the drugs, materials, or devices described in this manuscript. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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