Non-Alzheimer's dementia 2

Lewy body dementias

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The broad importance of dementia is undisputed, with Alzheimer's disease justifiably getting the most attention. However, dementia with Lewy bodies and Parkinson's disease dementia, now called Lewy body dementias, are the second most common type of degenerative dementia in patients older than 65 years. Despite this, Lewy body dementias receive little attention and patients are often misdiagnosed, leading to less than ideal management. Over the past 10 years, considerable effort has gone into improving diagnostic accuracy by refining diagnostic criteria and using imaging and other biomarkers. Dementia with Lewy bodies and Parkinson's disease dementia share the same pathophysiology, and effective treatments will depend not only on successful treatment of symptoms but also on targeting the pathological mechanisms of disease, ideally before symptoms and clinical signs develop. We summarise the most pertinent progress from the past 10 years, outlining some of the challenges for the future, which will require refinement of diagnosis and clarification of the pathogenesis, leading to disease-modifying treatments.

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This is the second in a **Series** of three papers about Non-Alzheimer's dementia

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Introduction

Dementia with Lewy bodies is a common type of dementia. Up to 80% of patients with Parkinson's disease progress to dementia.[1] These two clinical syndromes differ in the sequence of onset of dementia and parkinsonism, but with progression both syndromes and underlying pathological changes become similar and can be viewed as a continuum rather than dichotomous entities. They are known as Lewy body dementias (panel 1).

In this Review, we focus on advances since an important review[5] published in 2004, and the subsequent dementia with Lewy bodies consortium criteria.[2] The specificity of the consortium criteria[2] is generally good when core and suggestive features are present but sensitivity is only moderate. Accurate diagnosis is crucial for management because these patients need a specific treatment approach. Prospective clinicopathological investigations in both dementia with Lewy bodies and Parkinson's disease dementia have driven progress. More is known about pathogenic mechanisms and genetics, and there is increasing attention to prodromal stages and the use of biomarkers to support early and accurate diagnosis and management. We discuss the key issues that research should target to advance understanding of Lewy body dementias, improve diagnostic accuracy, and enhance treatment, which must include successful symptomatic and neuroprotective treatments.

Epidemiology

Both Parkinson's disease and dementia with Lewy bodies are age-related diseases, although onset before age 65 years is not uncommon and both diseases are more common in men than in women.

The point-prevalence of dementia is roughly 25% in patients with Parkinson's disease.[6] The risk of dementia increases with duration of disease and reaches 50% 10 years after diagnosis.[7] Most patients who survive for more than 10 years will develop dementia.[8] The incidence of dementia is roughly 100 per 1000 person-years; however, it is much lower during the first years after diagnosis.[9,10] Increasing age is a risk factor for the development of dementia in patient's with Parkinson's disease, and thus the time to dementia decreases with increasing age at onset of Parkinson's disease.[11]

There are fewer prevalence and incidence data for dementia with Lewy bodies. In a systematic review, estimates of the proportion of individuals with dementia with Lewy bodies ranged from 0 to 23% among people with dementia.[12] The mean prevalence of probable dementia with Lewy bodies was 4·2% in community-based studies and 7·5% in clinic-based studies. These values are probably underestimates, because the three studies that focused on identifying dementia with Lewy bodies and included a neurological examination showed higher proportions with the disease (16–24%).[12] In a population-based study, 7·6% of dementia cases were diagnosed as dementia with Lewy bodies.[13]

Dementia with Lewy bodies seems to be under-diagnosed in clinical practice.[14,15] Standardised scales focusing on the core features should be used. Furthermore, dopamine transporter imaging[16] and screening for rapid eye movement sleep behaviour disorder (RBD)[17] also increase the accuracy of diagnosis of dementia with Lewy bodies. Studies incorporating these methods suggest that 10–15% of people with dementia have dementia with Lewy bodies.[18,19]

In a study in the USA, the incidence of probable dementia with Lewy bodies was 3·5 per 100 000 person-years overall, and 31·6 per 100 000 person-years among people older than 65 years.[20] By contrast, a study in France estimated an incidence of 112 per 100 000 person-years in people aged 65 years and older.[21] One explanation for the difference is that the US study[20] included only patients who had a medical record diagnosis of a parkinsonian disorder, so people with mild or no parkinsonism would have been excluded. In the French study,[21] all participants were screened for symptoms of parkinsonism and cognitive impairment. In both studies,

Panel 1: **Dementia terminology**

Lewy body dementias
An umbrella term that includes clinically diagnosed dementia with Lewy bodies and Parkinson's disease dementia.

Dementia with Lewy bodies
Dementia that occurs before or concurrently with parkinsonism or within 1 year of onset of motor symptoms. However, not all patients develop parkinsonism.[2]

Parkinson's disease dementia
Dementia starting 1 year or more after well established Parkinson's disease.[1]

Mild cognitive impairment in Parkinson's disease
Cognitive impairment in patients with Parkinson's disease not sufficient to interfere greatly with functional independence.[3]

Lewy body disease
Pathological diagnosis. The distribution of Lewy body-type pathology and additional pathologies is often specified.

Major and mild neurocognitive disorder with Lewy bodies or due to Parkinson's disease
New terms proposed by DSM-5[4] corresponding to dementia with Lewy bodies and Parkinson's disease dementia.

DSM-5=Diagnostic and Statistical Manual of Mental Disorders, fifth edition.

core features of dementia with Lewy bodies were sought retrospectively, based on records, and presence of RBD was not assessed systematically, probably leading to underdiagnosis of dementia with Lewy bodies.

Pathogenesis

The hallmarks of Lewy body dementias are α-synuclein neuronal inclusions (Lewy bodies, and Lewy neurites), accompanied by neuronal loss. It is unclear whether Lewy bodies and Lewy neurites have a neuroprotective or neurotoxic role and to what extent they contribute to the clinical picture because some individuals have severe α-synuclein pathology at autopsy but no clinical symptoms of Lewy body dementia.[22] The underlying pathological cause of Lewy body dementias is probably multifactorial with factors that increase or decrease neural reserve also playing a part.

Braak and colleagues proposed a pathological staging of Parkinson's disease (with or without dementia) with Lewy body pathology starting in the dorsal IX/X motor nucleus or adjoining intermediate reticular zone, and spreading rostrally in the brainstem (substantia nigra, basal ganglia) then to the limbic system and subsequently to the neocortex.[23] The mechanism of the spread of the disease process is unknown but evidence suggests that α-synuclein pathology can spread from cell to cell.[24] However, some patients with dementia with Lewy bodies do not follow the caudorostral progression, suggesting that alternative patterns of spread are possible.[22] The proposed Braak staging excluded patients with dementia with Lewy bodies, and so the applicability of caudorostral progression to the disease is not established.

The pathological substrate of dementia in Lewy body dementias is also debated. Dementia can be present in patients with pure cortical α-synuclein pathology but the underlying pathology is often mixed.[25,26] Cortical α-synuclein pathology is the strongest candidate substrate for Parkinson's disease dementia, whereas amyloid β has a more prominent role in dementia with Lewy bodies.[27] However, even in Parkinson's disease dementia, the presence of cortical tau-containing neurofibrillary tangles and amyloid β pathology leads to more advanced dementia, implying that the two pathologies work together.[28] There is little evidence that cerebrovascular pathology contributes substantially to cognitive impairment in Parkinson's disease dementia. Vascular pathology often co-occurs with Alzheimer's disease pathology in dementia with Lewy bodies but the contribution of cerebrovascular disease to dementia with Lewy bodies has not been established.[29]

Genetics

The genetics of dementia with Lewy bodies, Parkinson's disease dementia, Parkinson's disease, and Alzheimer's disease overlap.[30] Most cases of Lewy body dementia seem to be sporadic but rare autosomal dominant inheritance has been reported, including mutations in the *SNCA* and *LRRK2* genes.[31] The mutations can manifest as Parkinson's disease, Parkinson's disease dementia, or dementia with Lewy bodies, suggesting that the different clinical phenotypes are on a spectrum of one underlying genetic–pathological entity.

There is evidence of familial aggregation of dementia with Lewy bodies.[32] Several studies, including one large multicentre study,[33] have shown that mutations in *GBA* are a significant risk factor for dementia with Lewy bodies and that carriers of mutations in *GBA* develop dementia with Lewy bodies at an earlier age than non-carriers, although another large study[34] did not confirm this finding. That study showed an association between *SNCA* and *SCARB2* and dementia with Lewy bodies.

The *APOE* ε4 allele, a strong risk factor for late-onset Alzheimer's disease, is also over-represented in sporadic Lewy body dementias compared with controls, but it is less common than in patients with Alzheimer's disease.[35] The *APOE* ε2 allele (the least common allele) might reduce the risk of developing dementia with Lewy bodies.[36]

Diagnosis and clinical symptoms

Panel 2 shows the diagnostic criteria for dementia with Lewy bodies and Parkinson's disease dementia. The biggest challenge in the diagnosis of dementia with Lewy bodies is early diagnosis and differentiation from Alzheimer's disease. In Parkinson's disease dementia, the main challenge is prediction and timely identification of cognitive impairment in patients with Parkinson's disease.

The current consortium criteria for dementia with Lewy bodies have been criticised for poor sensitivity. In 2861 patients from the National Alzheimer's Coordinating Center, sensitivity of clinical diagnosis against autopsy

was 32% and specificity was 95%.[38] The revised criteria of dementia with Lewy bodies[2] increased the proportion of cases fulfilling probable dementia with Lewy bodies criteria by 24%[39] by including suggestive features with additional diagnostic weighting. Diagnostic accuracy is higher when α-synuclein pathology is extensive, lower with increasing neuritic plaque pathology, and not affected by amyloid β load.[40]

Nevertheless, diagnostic accuracy is still only moderate in research and poor in clinical settings. Dementia with Lewy bodies is most often misdiagnosed as Alzheimer's disease. Including RBD as a core feature of disease improves sensitivity without sacrificing specificity.[17] Antipsychotic challenge should never be used for diagnosis because of associated morbidity. About half of patients with dementia with Lewy bodies react adversely to antipsychotics.[41] Fluctuating cognition is a particularly difficult clinical feature to elicit accurately. Fluctuation scales can be helpful but more studies of their reliability and validity are needed to standardise them.[42,43] In cases of dementia without parkinsonism, dementia with Lewy bodies is less likely to be considered, even though many patients with dementia with Lewy bodies never develop parkinsonism.

The sensitivity of the revised criteria could be improved by increasing the diagnostic weighting of some features, although this could lessen specificity. Upgrading visuospatial impairment to a core criterion could improve sensitivity because most patients with dementia with Lewy bodies have visuospatial impairment.[44] The specificity for dementia with Lewy bodies of visual hallucinations, parkinsonism, and fluctuating cognition is adequate only in mild-to-moderate dementia because these features are also common in late-stage Alzheimer's disease.[38] Visual hallucinations are typically well formed and usually feature people, children, or animals. Low dopamine transporter uptake on single photon emission CT improves the sensitivity and specificity of diagnosing dementia with Lewy bodies compared with Alzheimer's disease, but does not distinguish other parkinsonian

Panel 2: **Diagnostic criteria for dementia with Lewy bodies and Parkinson's disease dementia[1,2]**

Criteria for dementia with Lewy bodies

Central feature (required for possible or probable diagnosis)

- Progressive dementia severe enough to interfere with normal social or occupational function
- Deficits on tests of attention, executive function, and visuospatial ability might be especially prominent

Core features (two are required for probable, one for possible diagnosis)

- Fluctuating cognition, recurrent visual hallucinations, spontaneous parkinsonism

Suggestive features (any suggestive feature with at least one core feature defines probable dementia with Lewy bodies; any suggestive feature in the absence of core features defines possible dementia with Lewy bodies)

- Rapid eye movement sleep behaviour disorder, severe sensitivity to antipsychotics, low dopamine transporter uptake in the basal ganglia

Supportive features (commonly present but not proven to have diagnostic specificity)

- Repeated falls and syncope, transient unexplained loss of consciousness, severe autonomic dysfunction, non-visual hallucinations, systematised delusions, depression, relative preservation of medial temporal lobe structures, generalised low uptake on single photon emission CT perfusion or PET metabolism with reduced occipital activity, abnormal metaiodobenzylguanidine myocardial scintigraphy, prominent slow wave activity on electroencephalogram with temporal lobe transient sharp waves

A diagnosis of dementia with Lewy bodies is less likely if

- Cerebrovascular disease or other physical illness are sufficient to account for part or all of the clinical signs and symptoms
- Parkinsonism does not appear until severe dementia

Criteria for Parkinson's disease dementia[1]

Core features (both required for possible or probable Parkinson's disease dementia)

- Diagnosis of Parkinson's disease according to Queen Square Brain Bank Criteria[37]
- Dementia developing in the context of established Parkinson's disease, with cognitive impairment in more than one domain and severe enough to impair daily life

Associated clinical features (typical profile of cognitive deficits must be present for probable, but not possible, diagnosis)

- Typical cognitive profile: impairment in at least two of the following domains: (1) attention, which may fluctuate; (2) executive function; (3) visuospatial function; (4) free recall, which usually improves with cueing
- Presence of behavioural features supports but absence does not exclude diagnosis; includes apathy, depressed or anxious mood, hallucinations, delusions, and excessive daytime sleepiness

A diagnosis of Parkinson's disease dementia cannot be made if

- Cognitive and behavioural symptoms appear solely in the context of other conditions such as systemic diseases, drug intoxication, or major depression
- Patient meets criteria for probable vascular dementia

The temporal sequence of symptoms guides differential diagnosis of dementia with Lewy bodies and Parkinson's disease dementia

- In dementia with Lewy bodies, dementia develops before or within 1 year of spontaneous parkinsonism
- In Parkinson's disease dementia, dementia develops within the context of established Parkinson's disease

dementia syndromes such as progressive supranuclear palsy and corticobasal degeneration.[16,45]

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders[4] recognises dementia with Lewy bodies, termed "major neurocognitive disorder with Lewy bodies". Criteria are similar to the consortium criteria but the suggestive feature of low dopamine transporter uptake has been omitted, which is likely to compromise sensitivity. Investigations are listed separately, termed "suggestive features". However, they are subsumed under the heading "diagnostic markers" with unclear diagnostic weight.

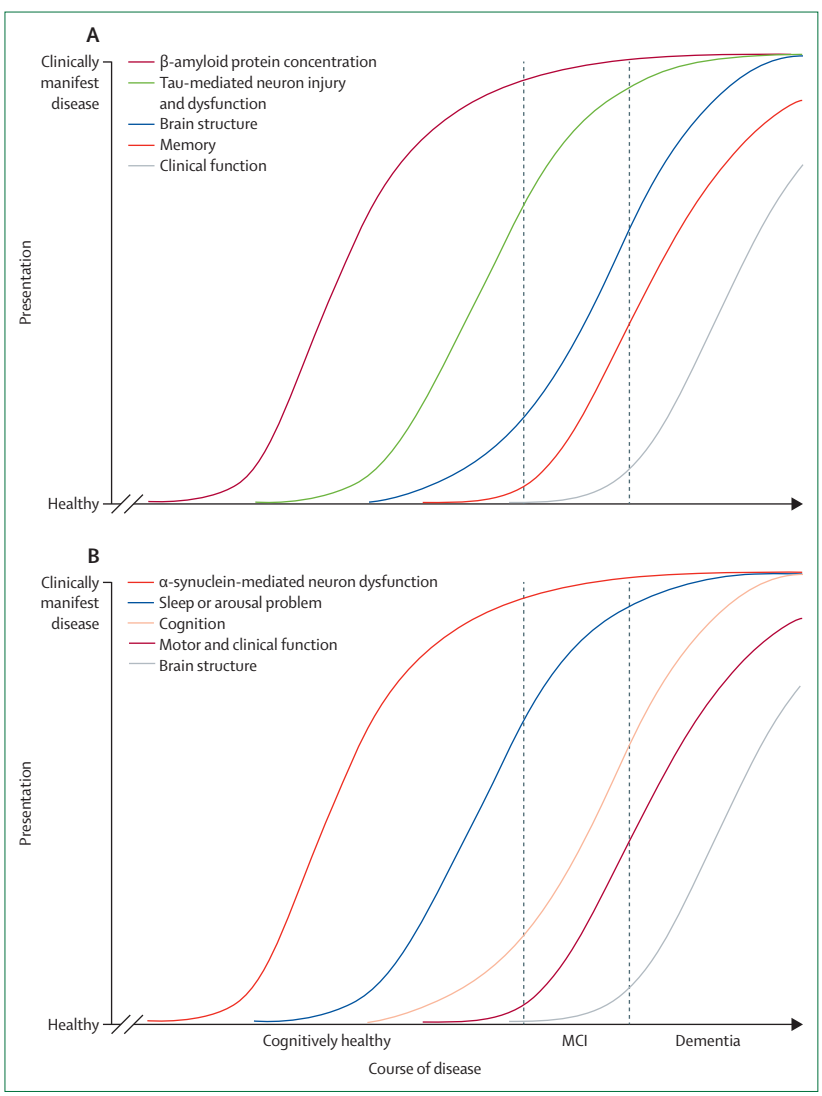

Figure 1: **Hypothetical model of prodromal dementia with Lewy bodies**
Shows dynamic changes in biomarkers associated with the progression of Alzheimer's disease and dementia with Lewy bodies. Based on retrospective data,[50] which used similar concepts and assumptions to the original model by Jack and colleagues for Alzheimer's disease.[51] (A) In patients with Alzheimer's disease, the progression of amyloid β deposition is detectable by changes in the concentrations of amyloid β 42 in cerebrospinal fluid or on PET imaging. These alterations precede changes in structural MRI and ^{18}F-fluorodeoxyglucose PET and other disease biomarkers, such as tau-mediated neuron injury and dysfunction (detected by cerebrospinal fluid concentrations of tau). (B) By contrast, in patients who have dementia with Lewy bodies (which is associated with α-synuclein-mediated neuronal dysfunction), altered sleep and arousal behaviour is often the earliest detectable change, followed by alterations in cognition and motor or clinical function. Reproduced from Fields and colleagues.[52] MCI=mild cognitive impairment.

The initial clinical presentations of Parkinson's disease dementia and dementia with Lewy bodies are distinct. Once dementia develops in Parkinson's disease; no clinical or biological differences can reliably distinguish it from dementia with Lewy bodies.

Prodromal and early Lewy body dementias

Cognitive impairment also occurs in patients with Parkinson's disease without dementia, termed mild cognitive impairment in Parkinson's disease (MCI-PD).[3] In cross-sectional samples, 20–25% of patients with Parkinson's disease without dementia can be classified as MCI-PD,[46] and MCI-PD is present in 15–20% of patients at diagnosis. This syndrome is associated with some degree of functional impairment and is a risk factor for incipient dementia,[47,48] although this risk might depend on the profile of cognitive impairment.

There is no consensus on how pre-dementia dementia with Lewy bodies should be defined. Given the complex clinical phenotype, the prodromal phase is probably heterogeneous.[49] Figure 1 shows a hypothetical model for the development of dementia with Lewy bodies. In patients with mild cognitive impairment, those with non-amnestic cognitive profile,[53] with parkinsonism or fluctuations,[54] with slowing on electroencephalography,[55] or problems with pentagon drawing[56] have an increased risk for developing dementia with Lewy bodies. In addition, patients with idiopathic RBD,[57] primary autonomic dysfunction,[58] and frequent delirium have increased risk of dementia with Lewy bodies.[59] Visual hallucinations in early or prodromal dementia are highly specific for a pathological diagnosis of dementia with Lewy bodies.[15] This finding is consistent with a study of patients with autopsy-confirmed dementia with Lewy bodies. Although few had visual hallucinations (22%), parkinsonism (26%), or both (13%) at the stage of mild dementia, visual hallucinations were the most specific feature differentiating dementia with Lewy bodies from Alzheimer's disease.[44]

Parkinsonism, visual hallucinations, olfactory dysfunction, constipation, increased salivation, and RBD are more common at the onset of dementia with Lewy bodies than of Alzheimer's disease.[60,61] 19 risk factors for Alzheimer's disease or Parkinson's disease were studied as potential risk factors for dementia with Lewy bodies.[62] A history of anxiety and depression was more common in patients with dementia with Lewy bodies than in cognitively healthy controls.

Neuropsychological aspects of Lewy body dementias

Panel 3 shows the neuropsychological domains and tests pertinent to Lewy body dementias. Characteristically, visuospatial and executive deficits with fluctuations in cognition and arousal are present in Lewy body dementias. Visuospatial or constructional impairment is present in 74% of patients with early-stage pathologically confirmed dementia with Lewy bodies compared with

45% of those with Alzheimer's disease,[44] and rarely in frontotemporal dementia.[77] The presence of early, severe visuospatial deficits in patients with suspected dementia with Lewy bodies predicts rapid decline and the development of visual hallucinations, and might identify patients whose clinical syndrome is due to Lewy bodies rather than Alzheimer's disease pathology.[78]

The cognitive profile of MCI-PD is heterogeneous, with many patients having executive, memory, or visuospatial impairments.[79] Executive dysfunction (deficits in selective attention, working memory, mental flexibility, planning, and reinforcement learning) can be prominent, and is primarily linked to nigrostriatal dopaminergic loss causing disruption of dorsolateral prefrontal–striatal circuitry.[80] Deficits on tests with a posterior cortical basis, specifically semantic fluency and figure copy, might herald subsequent dementia, whereas frontal-type executive deficits do not.[7] Once patients develop dementia, executive deficits are common and disabling, but of little use for differential diagnosis.[81,82]

Memory impairment does not preclude a diagnosis of dementia with Lewy bodies: patients with pure Lewy body disease have similar free recall but better delayed recognition memory than those with pure Alzheimer's disease or mixed pathology, suggesting impaired retrieval mechanisms.[83] Neocortical Lewy body pathology is related to yearly fluctuations on cognitive testing.[84] Mixed pathology complicates the neuropsychological profile, making it difficult to distinguish mixed Alzheimer's disease and dementia with Lewy bodies from pure Alzheimer's disease.

Cerebrospinal fluid and electroencephalography biomarkers

There is a drive to use biomarkers to enable preclinical, prodromal, and accurate clinical diagnosis and to monitor progression of disease and treatment effectiveness. Although Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies are synucleinopathies, authors of a systematic review[85] concluded that neither plasma nor cerebrospinal fluid α-synuclein are reliable biomarkers for Parkinson's disease. However, the concentration of α-synuclein in cerebrospinal fluid could be useful in dementia with Lewy bodies. A meta-analysis of 2728 patients showed that the mean cerebrospinal fluid α-synuclein concentration was significantly lower in patients with dementia with Lewy bodies than in those with Alzheimer's disease. No significant difference was recorded between dementia with Lewy bodies and Parkinson's disease or other neurodegenerative disorders.[86] Findings of a large longitudinal study of patients with Parkinson's disease[87] showed that lower baseline cerebrospinal fluid α-synuclein concentration predicted better preservation of cognitive function at follow-up.

Compared with Alzheimer's disease, for which cerebrospinal fluid biomarkers have been shown to have good sensitivity and specificity, the evidence for Lewy body dementias is insufficient for amyloid β 40–42, amyloid β 38, and amyloid β 42:amyloid β 38 ratio. Although amyloid β 1–42 concentrations cannot distinguish dementia with Lewy bodies from Alzheimer's disease, the amount of concomitant Alzheimer's pathology in dementia with Lewy bodies correlates with amyloid β 1–42 but not with total tau concentrations in neuropathologically defined patients.[88] Similarly, reduced amyloid β 1–42 concentrations also occur in Parkinson's disease dementia[89] and MCI-PD, and in prospective studies, amyloid β 1–42 concentrations predicted future cognitive decline and early dementia.[90,91]

Additional markers might also have relevance. For example, plasma concentrations of epidermal growth factor can predict cognitive decline in Parkinson's disease.[92] Low background rhythm frequency ascertained with quantitative electroencephalogram is associated with cognitive impairment in Parkinson's disease and can also predict the development of dementia in Parkinson's disease.[93] Similarly, slow wave activity is common to all dementias but it is most prominent in dementia with Lewy bodies,[94] and characteristic abnormalities can even precede the appearance of distinctive clinical features.[95]

Imaging

Most patients with suspected dementia with Lewy bodies or Parkinson's disease dementia will have a CT or MRI scan as part of basic clinical investigations. But the number of imaging techniques that can be used in the diagnostic assessment is growing.

In both Parkinson's disease dementia and dementia with Lewy bodies, a structural MRI has little value for the differential diagnosis from other dementias (table 1). Other techniques include perfusion single photon emission CT and metabolic PET. Occipital hypometabolism is the most distinct finding in dementia with

Panel 3: **Recommended guidelines for cognitive test selection in Lewy body disorders[3]**

Brief screening tools

Montreal Cognitive Assessment,[63] Parkinson's Disease Cognitive Rating Scale,[64] Parkinson's Neuropsychometric Dementia Instrument,[65] Scales for Outcomes in Parkinson's Disease—Cognition[66]

Visuospatial

Figure copy tests (eg, cube, clock, interlocking pentagons, or complex figures), spatial judgment tests that do not rely on motor functions (eg, Visual Object Space Perception Battery,[67] Benton Judgment of Line Orientation)[68]

Executive or attention

Measures of working memory, selective attention, set-shifting, planning, and verbal fluency (eg, Wisconsin Card Sorting Test,[69] NIH EXAMINER,[70] trail making test,[71] Stroop[72])

Memory

Word list, figure, or associative learning with delayed recall and recognition (eg, Rey Auditory Verbal Learning Test,[73] California Verbal Learning Test,[74] Free and Cued Selective Reminding Test,[75] Brief Visuospatial Memory Test-Revised[76]); visual memory might be poor for reasons of visual perceptual or memory deficit.

	Dementia with Lewy bodies	Parkinson's disease dementia	Comment
MRI			
Atrophy	Diffuse pattern of global grey matter atrophy compared with healthy controls;[96] less medial temporal lobe atrophy than Alzheimer's disease; atrophy increases with Alzheimer's disease pathology[97]	Greater atrophy of medial temporal lobe, frontal lobes, and temporal lobes compared with healthy controls;[98] dementia severity correlates with medial temporal lobe atrophy	If medial temporal lobe preserved, supports dementia with Lewy bodies diagnosis; if medial temporal lobe atrophied, not diagnostically helpful
Diffusion	Loss of parieto-occipital white matter integrity compared with healthy controls[99]	Changes in frontal, temporal, and occipital white matter diffusivity relative to healthy controls[98]	Not diagnostically useful
SPECT			
Dopamine transporter	Significantly reduced uptake in caudate and putamen relative to healthy controls or patients with Alzheimer's disease[16,45]	Significantly reduced uptake in caudate and putamen relative to healthy controls or patients with Alzheimer's disease (but is never clinically indicated)	FP-CIT SPECT scan diagnostically useful for distinguishing dementia with Lewy bodies from Alzheimer's disease or healthy controls; dopaminergic dysfunction does not distinguish between Parkinson's disease dementia, dementia with Lewy bodies, and other parkinsonian syndromes (corticobasal degeneration and progressive supranuclear palsy)
Perfusion	Global cortical hypoperfusion relative to healthy controls; some evidence for reduced occipital lobe perfusion relative to Alzheimer's disease but findings unreliable[100]	Global cortical hypoperfusion relative to healthy controls; visual cortex hypoperfusion relative to Alzheimer's disease[98]	Occipital hypoperfusion a supportive diagnostic feature for dementia with Lewy bodies (common but not specific)
SPECT and PET			
Cholinergic	Reduced cortical acetylcholinesterase activity relative to healthy controls or patients with Alzheimer's disease; increased muscarinic and nicotinic receptors in occipital lobe relative to healthy controls[100]	Reduced cortical acetylcholinesterase activity relative to healthy controls or patients with Alzheimer's disease; increased muscarinic receptors in occipital lobe relative to healthy controls	Not diagnostically useful; cholinergic dysfunction accounts for effectiveness of acetylcholinesterase inhibitors in Lewy body dementia
PET			
Glucose metabolism	Reduced occipital lobe metabolism relative to Alzheimer's disease[96]	Greater visual cortex hypometabolism relative to Alzheimer's disease	Supportive diagnostic feature for dementia with Lewy bodies; occipital hypometabolism predicts development of dementia in Parkinson's disease; helpful when frontotemporal dementia with reduced dopamine transporter uptake is a possibility
Amyloid	Greater amyloid deposition compared with healthy controls or patients with Parkinson's disease dementia, but less than in those with Alzheimer's disease[101]	Parkinson's disease dementia less than dementia with Lewy bodies, but more than mild cognitive impairment in Parkinson's disease[102]	Not diagnostically useful; might help identify patients for treatment with antiamyloid drugs in the future

FP-CIT SPECT=^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane single photon emission CT.

Table 1: **Neuroimaging in Lewy body dementias**

Lewy bodies compared with Alzheimer's disease and healthy controls (both Alzheimer's disease and dementia with Lewy bodies show temporoparietal hypometabolism). Reduced occipital metabolism and perfusion are supportive features in the 2005 consensus criteria[2] for dementia with Lewy bodies, and occipital hypometabolism can distinguish dementia with Lewy bodies from Alzheimer's disease and healthy controls with high sensitivity and specificity.[103,104] Kantarci and colleagues[105] reported an association between occipital hypometabolism and the frequency of visual hallucinations. However, occipital hypometabolism is not always present in neuropathologically confirmed disease.[106] The posterior cingulate island sign, which reflects relatively preserved metabolism in the posterior cingulate region, is sensitive and specific for dementia with Lewy bodies.[107,108] Patients with Parkinson's disease dementia also have hypometabolism in frontal, parietal, and occipital regions.[109]

^{123}I-metaiodobenzylguanidine scintigraphy, a marker of postganglionic cardiac sympathetic innervation, shows promise as a biomarker of dementia with Lewy bodies. A meta-analysis[110] of 46 studies involving 2680 patients with neuropsychiatric and movement disorders showed that it reliably distinguished between patients with Lewy body dementias and patients with Alzheimer's disease. A large Japanese multicentre study[111] using consensus diagnosis of dementia with Lewy bodies showed good sensitivity and specificity, similar to dopamine transporter imaging.

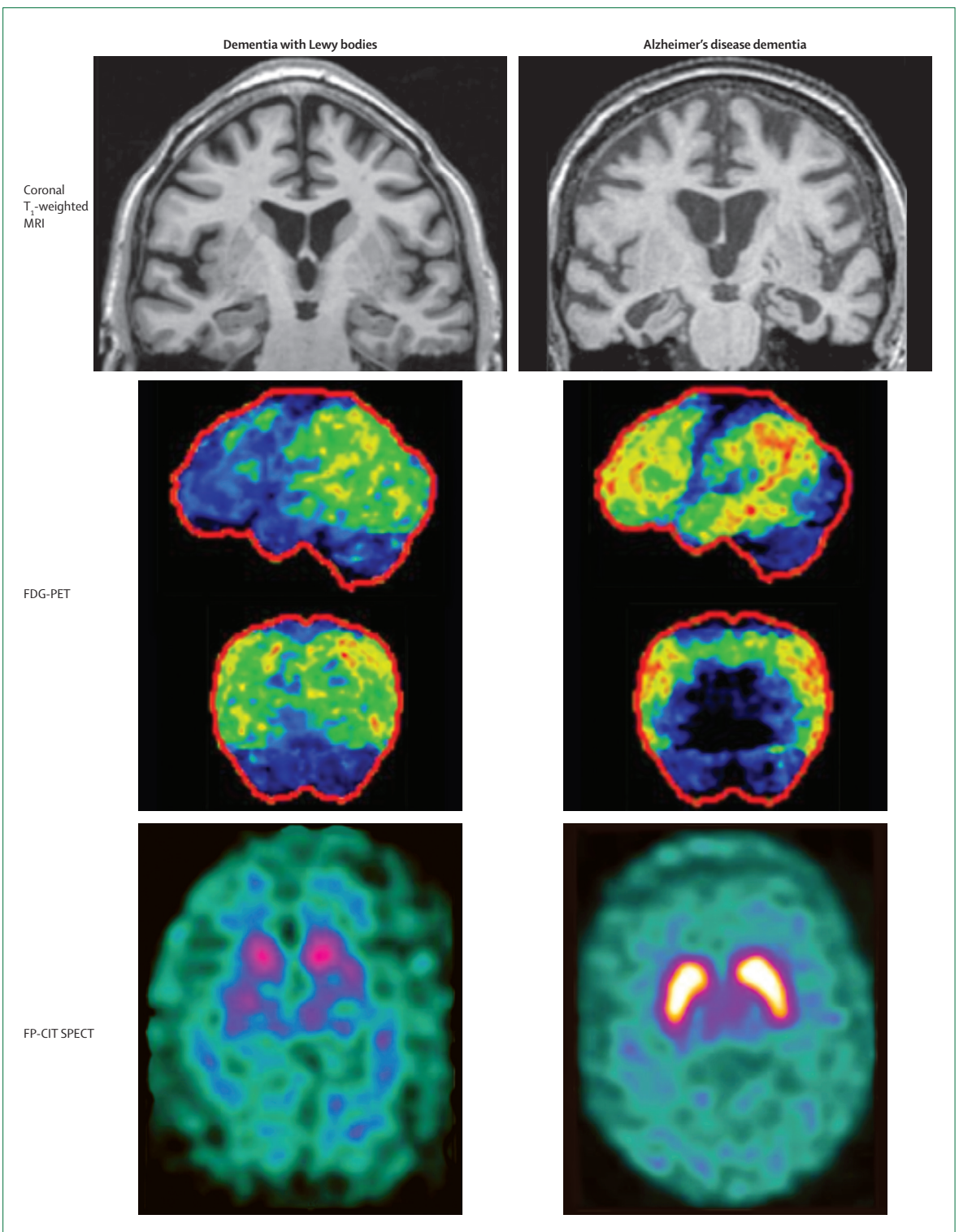

Figure 2: **Representative neuroimaging in dementia with Lewy bodies and dementia in Alzheimer's disease**
FDG-PET=^{18}F-fluorodeoxyglucose PET. FP-CIT SPECT=^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane single photon emission CT. Note the lack of hippocampal atrophy on MRI, presence of occipital hypometabolism on FDG-PET, and reduced striatonigral uptake on FP-CIT SPECT in dementia with Lewy bodies, compared with the findings in Alzheimer's disease. Images courtesy of Clifford Jack, Kejal Kantarci, and Val Lowe.

Patients with substantial cardiac disease or poorly controlled diabetes were excluded. Clinicians should be aware that the presence of cardiac disease and diabetes needs to be taken into consideration when ^{123}I-metaiodobenzylguanidine scintigraphy is done to avoid false positives.

Low dopamine transporter uptake in basal ganglia is a suggestive feature in the consensus criteria for dementia with Lewy bodies. The ligand most often studied is ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) in single photon emission CT. It has high sensitivity and specificity for dementia with Lewy bodies in both clinically (consensus panel) and pathologically diagnosed cases, and possible dementia with Lewy bodies.[16,112–114] A meta-analysis[115] of four studies with 419 patients showed high diagnostic accuracy of FP-CIT, and a Cochrane review[116] concluded that semiquantitative analysis of scans seemed to be more accurate than visual rating. However, some caution is needed. Although a normal FP-CIT scan does exclude a diagnosis of Parkinson's disease dementia, it does not exclude a diagnosis of dementia with Lewy bodies. 3–9% of patients who have dementia with Lewy bodies have cortical and limbic pathology without nigrostriatal pathology (false negative). Rarely, diagnoses will be false positive. About a third of patients with frontotemporal dementia have an abnormal (positive) FP-CIT scan and could therefore be mistaken for dementia with Lewy bodies.[117] Also, most patients with progressive supranuclear palsy and corticobasal degeneration have abnormal (positive) FP-CIT uptake. However, it should be possible to separate dementia with Lewy bodies from frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration on clinical grounds. Therefore, FP-CIT imaging might be particularly useful when the typical clinical features of frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration are absent and the primary diagnostic consideration is dementia with Lewy bodies or Alzheimer's disease. Figure 2 shows examples of findings on MRI, FDG-PET, and FP-CIT single photon emission CT.

In the past 5 years, amyloid imaging studies have proliferated. Most used ^{11}C-Pittsburgh compound B but ^{18}F-labelled ligands are also available. Overall, patients with dementia with Lewy bodies have higher amyloid retention than do patients with Parkinson's disease dementia and healthy controls but lower than patients with Alzheimer's disease.[102] The presence of amyloid deposition has little value in separating dementia with Lewy bodies from Alzheimer's disease,[118] but increased amyloid load is associated with the development of dementia in Parkinson's disease and with faster cognitive decline in dementia with Lewy bodies.[101] Testing for amyloid load in Lewy body dementias might be important when treatments that target specific pathology become available.

RBD

RBD is a parasomnia characterised by abnormal vocalisations, motor behaviour, and dream mentation, in which patients seem to act out their dreams by yelling, screaming, flailing limbs, punching, and kicking.[119,120] Such dreams typically involve a perceived attacker such as a human, animal, or insect, towards which the vocalisations and limb movements are directed. While a formal diagnosis needs confirmation of increased electromyographic tone with or without dream enactment behaviour on polysomnography, a strong suspicion of RBD can be ascertained by history, and several simple and accurate questionnaires are available.[121]

RBD is relevant to Lewy body disease for many reasons. It is strongly associated with α-synucleinopathies. The presence of RBD increases the diagnostic likelihood of synucleinopathy-spectrum disorders compared with Alzheimer's disease and the primary tauopathies.[122] Prospective analyses have shown that 70–90% of patients with RBD develop dementia (usually dementia with Lewy bodies) or parkinsonism (usually Parkinson's disease) within 15 years.[123–125] RBD arises from pathology in the brainstem circuitry involved in the control of rapid eye movement sleep. Although the pathophysiology of human RBD remains unclear, degeneration of the subcoeruleus region or magnocellular reticular formation (or both) has been proposed to be responsible. These regions are affected by Lewy body disease and, according to the Braak staging, are involved earlier than the substantia nigra, limbic system, and neocortex.[126] This pattern of development of pathology would explain why RBD often precedes the typical motor, cognitive, and neuropsychiatric manifestations of Lewy body dementias by years or decades.[127,128]

Management

Management of patients with Lewy body dementias is challenging. There are no disease-modifying drugs so treatment is directed towards symptoms; however, very few randomised controlled trials of treatments exist. The range of problematic manifestations of Lewy body dementias, along with high sensitivity to drug-induced adverse events and the likelihood that some drugs might improve one symptom but worsen others, contribute to the difficulties of management. One needs to be extremely cautious with all forms of treatment for patients with Lewy body dementias. Despite these challenges, comprehensive management is feasible by identifying and prioritising target features and then applying evidence-based measures (table 2).[129,131–133] In general, careful dosing and monitoring schedules are recommended.

The acetylcholinesterase inhibitor rivastigmine moderately benefits cognition, neuropsychiatric symptoms, and activities of daily living in patients with Parkinson's disease dementia,[134] whereas donepezil showed mixed results in a large randomised controlled trial.[135] In dementia with Lewy bodies, rivastigmine improved

	Evidence in dementia with Lewy bodies	Evidence in Parkinson's disease dementia	Comments
Cognition			
Acetylcholinesterase inhibitors	Efficacious	Efficacious	Rivastigmine and donepezil class 1 efficacy in dementia with Lewy bodies; Cochrane review of dementia with Lewy bodies, Parkinson's disease dementia, and MCI-PD showed overall positive effect
Memantine	Insufficient evidence	Insufficient evidence	Small significant improvement in overall clinical impression
Parkinsonism			
Levodopa	Insufficient evidence	Insufficient evidence	Levodopa replacement less effective in dementia with Lewy bodies than in Parkinson's disease; probable increased risk of psychosis in patients with dementia with Lewy bodies
Hallucinations			
Acetylcholinesterase inhibitors	Insufficient evidence	Insufficient evidence	No randomised controlled trials have assessed hallucinations; other evidence is positive
Antipsychotic drugs	Unlikely to be efficacious	Mixed	In treatment of psychosis associated with Parkinson's disease and Parkinson's disease dementia, clozapine is effective and olanzapine ineffective; the evidence for quetiapine is mixed
Depression or anxiety			
Antidepressant drugs	Insufficient evidence	Insufficient evidence	Evidence mixed; some beneficial effect with venlafaxine, paroxetine, and nortriptyline in Parkinson's disease
RBD			
Melatonin	Insufficient evidence	Insufficient evidence	Evidence in Parkinson's disease from non-randomised trials
Clonazepam	Insufficient evidence	Insufficient evidence	Non-randomised controlled trial evidence positive
Excessive daytime sleepiness			
Modafinil	Insufficient evidence	Insufficient evidence	Evidence in Parkinson's disease from randomised controlled trials; non-randomised trial evidence in dementia with Lewy bodies
Urinary symptoms			
Trospium	Insufficient evidence	Insufficient evidence	No randomised controlled trials reported but does not cross blood–brain barrier so in theory should be preferable to oxybutynin
Postural hypotension			
Fludrocortisone	Insufficient evidence	Insufficient evidence	No evidence from randomised controlled trials, but other evidence positive in both Parkinson's disease dementia and dementia with Lewy bodies

MCI-PD=mild cognitive impairment in Parkinson's disease. RBD=rapid eye movement sleep behaviour disorder.

Table 2: **Evidence for treatment of dementia with Lewy bodies and Parkinson's disease dementia**[129,130]

attention and memory in a small study,[136] but did not affect Mini-Mental State Examination score or clinical impression. More convincing findings were reported in two large placebo-controlled studies,[137,138] which showed efficacy both on Mini-Mental State Examination score and clinical global impression of change after 12 weeks on 5 mg and 10 mg donepezil. These improvements were maintained for 52 weeks in both studies.[139,140] A Cochrane review[132] concluded that acetylcholinesterase inhibitors are beneficial for patients with Parkinson's disease dementia. Gastrointestinal side-effects were common, but no overall worsening of motor symptoms was noted. Thus, we recommend that acetylcholinesterase inhibitors, in particular rivastigmine and donepezil in standard doses, are used in Lewy body dementias.[132]

Some[141] but not all[142] studies have shown that memantine is modestly efficacious for overall impression of change, including for RBD, in patients with Lewy body dementias.[143] Mixed results have been reported in smaller studies, but a meta-analysis suggested that there is an overall improvement with memantine in Lewy body disorders.[144,145] Drugs with substantial anticholinergic properties are discouraged because of the risk of cognitive worsening and delirium.

Dopaminergic antiparkinsonian drugs can worsen visual hallucinations and other neuropsychiatric features, and thus reducing the dose of such drugs should be the first consideration. If this is not successful, there is good evidence that clozapine can reduce visual hallucinations in Parkinson's disease. However, severe dementia is a common exclusion criterion in these studies[146] and only two studies[147,148] included patients with Parkinson's disease and cognitive impairment but did not report data on the subgroup of patients with Parkinson's disease dementia. The use of clozapine is limited because of its potential to induce agranulocytosis and the necessity for regular blood monitoring.

Several open-label studies have suggested that quetiapine is useful in dementia with Lewy bodies, but the only placebo-controlled study was small and reported no effect on agitation and psychosis.[149] There were no differences on a psychosis scale between quetiapine and

placebo. The authors noted a large effect in the placebo group. Quetiapine was generally well tolerated.

Severe hypersensitivity reactions to antipsychotics with motor and cognitive worsening can occur in all forms of Lewy body dementias. In addition, strokes and other risks associated with the use of antipsychotics are more likely in elderly people with dementia. Although little positive evidence supports the use of antipsychotics for Lewy body dementias, many clinicians still use clozapine or quetiapine to treat psychotic symptoms. One promising new drug is pimavanserin, a selective serotonin 5-HT_{2A} inverse agonist, which significantly reduced psychotic symptoms in patients with Parkinson's disease and was well tolerated in a randomised controlled trial.[150] Patients had a mean Mini-Mental State Examination score of 26, and thus most patients did not have dementia.

There is no systematic evidence that acetylcholinesterase inhibitors can improve visual hallucinations in patients with Parkinson's disease, although they might be particularly effective in patients with Parkinson's disease dementia who have visual hallucinations.[151] Incident visual hallucinations were less common in patients with Parkinson's disease dementia receiving rivastigmine than in those receiving placebo,[134] suggesting a possible preventive effect. In dementia with Lewy bodies, rivastigmine reduced a summary scale of four neuropsychiatric symptoms (delusions, visual hallucination, apathy, and depression) by 30% compared with placebo.[136] These symptoms also improved with donepezil.[139] However, these studies did not specifically recruit patients with troublesome visual hallucinations; therefore, new, safe, and effective treatments for psychotic symptoms in patients with Lewy body dementias are needed. To conclude, for patients with visual hallucinations, if reducing dopaminergic drugs is not feasible, a practical option would be to start treatment with an acetylcholinesterase inhibitor. If symptoms do not improve and treatment is strongly indicated, low doses of quetiapine or clozapine (12·5–50 mg per day) could be considered (while waiting for results of pimavanserin trials), but need to be carefully monitored and withdrawn if no response occurs or troublesome adverse events occur.

Antidepressants might improve depression in patients with Parkinson's disease,[152] but people with dementia are usually excluded from trials and no evidence from randomised controlled trials is available in patients with Parkinson's disease dementia or dementia with Lewy bodies. Antidepressants with prominent anticholinergic effects should be avoided. Psychostimulants (eg, methylphenidate, dextroamphetamine) and wake-promoting drugs (eg, modafinil, armodafinil) are used in clinical practice, but their effectiveness for apathy and drowsiness in patients with Lewy body dementia is unknown.

Although dopamine replacement treatment for Parkinson's disease is well established, no trials have focused on Parkinson's disease dementia, and it is generally considered to be less effective and have more side-effects in this group than in patients with Parkinson's disease who do not have dementia. Similarly, no trials have been done in patients with dementia with Lewy bodies, but levodopa has been reported to improve parkinsonism in uncontrolled studies of dementia with Lewy bodies, although the response varies compared with that in Parkinson's disease.[153] Even less is known about dopamine agonists. Side-effects (especially exacerbation of visual hallucinations or delusions) restrict their usefulness in dementia with Lewy bodies. Nevertheless, in patients with clinically significant parkinsonism, levodopa slowly titrated from 50 mg per day up to 300–600 mg per day should be considered, with close monitoring of side-effects.

Improving safety is the mainstay of management of RBD, including moving sharp objects away from the bed and placing a foam mattress on the floor next to the bed to minimise injury from falling or jumping off the bed. When necessary, low doses of clonazepam or melatonin, or both, can be effective.[154] Memantine or acetylcholinesterase inhibitors improve RBD in some cases.[143] Hypersomnia is also common in patients with Lewy body dementias, due to varying degrees of nocturnal sleep fragmentation, sleep apnoea, periodic limb movements and associated arousals, and alterations in the intrinsic sleep–wake physiology. Treatment of these causes of hypersomnia should be considered, including nasal continuous positive airway pressure for obstructive sleep apnoea and dopaminergic or other drugs for management of periodic limb movements. Wake-promoting drugs such as modafinil can be used for hypersomnia, but they have not been tested in randomised controlled trials. Insomnia can be treated with low doses of melatonin, sedatives or hypnotics, or mirtazapine (but mirtazapine can aggravate RBD).

For management of autonomic dysfunction, non-pharmacological treatments include increasing salt in the diet, use of compression stockings or an abdominal binder for orthostatic hypotension, elevation of the head of the bed during sleep to promote vasomotor tone while minimising supine hypertension, and increasing fluid intake and fibre in the diet for constipation. Dopaminergic drugs and atypical antipsychotics can exacerbate orthostatic hypotension; dose decreases are sometimes needed. Antihypertensive drugs can be withdrawn. Cholinergic stimulation in the gut from acetylcholinesterase inhibitors, which can cause diarrhoea in some patients, can ameliorate constipation in patients with Lewy body disease. Many drugs prescribed for urinary incontinence have anticholinergic activity and the potential benefit needs to be weighed against risk of cognitive worsening and delirium.

Despite no systematic evidence for the use of non-pharmacological strategies, cognitive behavioural therapy is effective for depression in patients with

Panel 4: **Ten priorities and challenges for Lewy body disease research**

Criteria
Although the initial clinical presentations of Parkinson's disease dementia and dementia with Lewy bodies are distinct, and patients with Parkinson's disease have historically been studied by movement specialists and those with dementia with Lewy bodies by behaviour specialists, it is now clear that they are two entities on a spectrum of Lewy body disorder. At present, the research criteria for dementia with Lewy bodies and Parkinson's disease dementia are separate, but in the future a single set of criteria capturing the similarities and differences might be more appropriate. With new evidence, present core and suggestive features might carry different diagnostic weights, which could be captured in new criteria. The weight of individual investigations perhaps needs to be specified.

Terminology
The DSM-5[4] is a clear advance in that it now acknowledges the existence of Lewy body dementias and provides a common framework for the diagnosis of neurocognitive disorders,[161] but perhaps an opportunity was missed to also incorporate more recent knowledge to update the criteria to accord with the newly proposed criteria for Alzheimer's disease and prodromal Alzheimer's disease.

Risk factors, earliest signs, and prodromal stages
The pathology and individual clinical features (rapid eye movement sleep behaviour disorder, subtle visuoperceptual deficit, autonomic dysfunction, dopaminergic imaging abnormalities) are present before the full emergence of symptoms. Their addition to the criteria should be considered. Longitudinal cohorts enriched with individuals with potential early manifestations of dementia with Lewy bodies and culminating in autopsy studies are needed to identify new biomarkers for earlier diagnosis and to make possible the assessment of neuroprotective treatments.[162]

Multicentre randomised controlled trials of preventive measures
There are no randomised controlled trials of preventive measures, and more trials are needed to assess treatment response for the various symptoms and overall progression of the illness.

Pathological staging
Although the pathological staging for Parkinson's disease and Parkinson's disease dementia is well established, the underlying pathology and the appropriate staging in dementia with Lewy bodies are important areas for future research. This would be greatly facilitated by large prospective studies with brain donation programmes.

Imaging
Imaging the dopaminergic pathways is a helpful surrogate for the underlying Lewy body pathology, but ligands are needed for α-synuclein, the most likely pathological substrate for Lewy body disorders. Extracellular α-synuclein can directly activate microglia, which can be imaged with ^{11}C-PK11195 and PET. Imaging of amyloid, tau, cholinergic dysfunction, and neuroinflammation is also likely to clarify the contribution of different pathologies to the clinical picture.

New biomarkers
Biomarkers are increasingly becoming part of the diagnostic tests in patients with pre-dementia and early dementia diagnosis. Evidence for novel biomarkers (eg, plasma concentrations of epidermal growth factor[92] and plasma apolipoprotein A1[163]) need further independent confirmation in large, prospective studies. Extracellular α-synuclein might be the pathological substrate of Lewy body disorders. Extracellular α-synuclein is, therefore, a promising therapeutic target.[164]

Genetics
Whole exome sequencing to identify DNA changes relevant to Lewy body dementias is possible and should be the subject of large international studies. Such studies would identify individuals most at risk of Lewy body dementias likely to benefit from neuroprotective treatment.

Development of new treatment targets
Work to develop α-synuclein-based targets, including vaccine strategies, are underway. For example, immunisation with full-length human α-synuclein protein in a mouse model of Parkinson's disease can decrease the accumulation of the aggregated forms of this protein in neurons and reduce neurodegeneration.[165] Confirmation in human beings is eagerly awaited.

Symptomatic treatment
The positive response of psychosis to pimavanserin in patients with Parkinson's disease but without dementia[150] suggests that this drug should be investigated in people with Lewy body dementias. Randomised controlled trials are needed to assess the efficacy in Lewy body dementias of several drugs used to treat depression, parkinsonism, excessive daytime sleepiness, rapid eye movement sleep behaviour disorder, impotence, urinary incontinence, and orthostatic hypotension.

DSM-5=Diagnostic and Statistical Manual of Mental Disorders, fifth edition.

Parkinson's disease.[155] However, cognitive impairment probably reduces feasibility of this treatment and is an exclusion criterion in many studies. Coping mechanisms for visual hallucinations might help some patients. Education and support to caregivers are important.

Future research

As for other neurodegenerative disorders, developing new drugs with disease-modifying effects is the most urgent need in Lewy body dementia. Numerous pathways and targets are being explored for Parkinson's disease and Alzheimer's disease, and strategies targeting the

misfolding of proteins such as tau, amyloid, and α-synuclein are also likely to be relevant for dementia with Lewy bodies and Parkinson's disease dementia. Modulating α-synuclein toxicity, for example by targeting heat shock proteins[156,157] or by manipulating chaperone-mediated autophagy,[158] are promising strategies. Alternative strategies include potential neuroprotective drugs such as adenosine-receptor blockers, monoamine oxidase inhibitors, antioxidative drugs, nerve growth factor, and stem-cell therapy, and multi-target drugs with neuroprotective and neurorestorative activity.[159] However, several challenges need to be overcome before such strategies can be successfully introduced.[160] Improving diagnosis by developing new biomarkers, better understanding of genetics, clarifying terminology and criteria, and determining protective and risk factors are all important (panel 4).

Conclusions

Our understanding of Lewy body dementias has progressed greatly over the past 10 years. Despite the criticism of the 2005 consensus criteria for their poor sensitivity, they have led to major advances in understanding of dementia with Lewy bodies and refinement of diagnostic accuracy and management. At the same time, the realisation that patients with Parkinson's disease often develop cognitive deficits and dementia has also led to extensive research efforts and new diagnostic criteria for Parkinson's disease dementia and MCI-PD. Several challenges remain. Perhaps the next step is for all interested parties to participate in the next international workshop meeting on dementia with Lewy bodies and to also include Parkinson's disease dementia and develop new consensus criteria for Lewy body dementias that incorporate not only dementia but also the prodromal and preclinical phases of Lewy body dementias.

Contributors

All the authors planned the seminar, wrote and edited the report, and the final version.

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