REVIEW ARTICLE

Lewy Body Dementias

By Melissa J. Armstrong, MD, MSc, FAAN

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

SUPPLEMENTAL DIGITAL CONTENT (SDC) AVAILABLE ONLINE

CITE AS:
CONTINUUM (MINNEAP MINN) 2019;25(1, DEMENTIA):128–146.

Address correspondence to Dr Melissa J. Armstrong, Department of Neurology, University of Florida College of Medicine, McKnight Brain Institute, L3-100 MBI, PO Box 100236, Gainesville, FL 32610, *melissa.armstrong@neurology.ufl.edu*.

RELATIONSHIP DISCLOSURE:
Dr Armstrong serves on the evidence review board of *Neurology* journals and as a guideline consultant for the American Academy of Neurology and has received personal compensation for speaking engagements from the American Academy of Neurology and Medscape CME.
Continued on page 146

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Armstrong discusses the unlabeled/investigational use of biomarkers for the diagnosis of dementia with Lewy bodies and the unlabeled/investigational use of donepezil, galantamine, and memantine for cognitive symptoms in Lewy body dementia; clozapine and quetiapine for psychosis in Lewy body dementia; and clonazepam and melatonin for rapid eye movement sleep behavior disorder.

ABSTRACT

PURPOSE OF REVIEW: This article describes current diagnostic criteria relating to the diagnosis of Lewy body dementia, highlights diagnostic controversies, and reviews treatment approaches.

RECENT FINDINGS: Clinical diagnostic criteria for both Parkinson disease and dementia with Lewy bodies have been recently updated. These criteria result in overlap between individuals diagnosed with Parkinson disease and those with dementia with Lewy bodies. Although clinical features and symptomatic treatment overlap, differences remain in epidemiology and expected progression. The high prevalence of cognitive impairment in Parkinson disease supports regular screening for cognitive changes and counseling patients and families regarding what to expect. Treatment for Lewy body dementia involves avoiding medications that may cause or exacerbate symptoms; prescribing pharmacologic agents to address bothersome cognitive, behavioral, movement, and other nonmotor symptoms; recommending physical exercise and therapy; and providing education, counseling, caregiver support, and palliative care.

SUMMARY: Lewy body dementia includes both dementia with Lewy bodies and Parkinson disease dementia, overlapping clinicopathologic entities with differences relating to diagnosis and expected progression. Treatment is symptomatic and thus largely overlapping for the two conditions.

INTRODUCTION

Lewy body dementia is an umbrella term that includes the clinical diagnoses of both Parkinson disease (PD) dementia and dementia with Lewy bodies (DLB), making it the second most common degenerative dementia after Alzheimer disease (AD).[1] The nomenclature includes the following:

- **Lewy body dementia: An umbrella term for a clinical diagnosis of either PD dementia or DLB**
- **Parkinson disease dementia: Dementia occurring in the context of an established diagnosis of PD**
- **Dementia with Lewy bodies: Dementia associated with some combination of fluctuating cognition, recurrent visual hallucinations, rapid eye movement (REM) sleep behavior disorder (RBD), and parkinsonism starting with or after the dementia diagnosis**
- **Lewy body disease: A pathologic diagnosis based on the identification of Lewy body pathology on postmortem examination**

The clinical diagnoses of PD dementia and DLB are distinct from Lewy body disease, a pathologic diagnosis assigned when Lewy bodies (neuronal

α-synuclein inclusions) and neuronal loss are identified on postmortem examination, independent of clinical presentation. Lewy body disease has multiple types, including brainstem predominant, transitional (limbic), and diffuse (neocortical) forms, associated with increasing degrees of pathologic burden.

While this categorization seems straightforward on the surface, physicians, scientists, patients, and families alike can be confused by the nuanced distinctions between Lewy body terms. More than one patient and family have announced with concern that they have had the wrong diagnosis for years, labeled with PD only to find that what they really have is "Lewy body." Such commonly encountered confusion underscores the importance of precision in how clinical and pathologic terms are used and clarity when explaining overlapping vocabulary to patients and families.

The situation is made more challenging by ongoing updates in the clinical diagnostic criteria for both PD and DLB that impact how these diseases are identified and diagnosed. Historically, the presence of dementia within the first year of the onset of parkinsonian symptoms was an exclusion criterion for the diagnosis of idiopathic PD and considered more suggestive of an alternative diagnosis such as DLB. In 2015, however, the International Parkinson and Movement Disorder Society released new clinical diagnostic criteria for PD that dispensed with the 1-year rule.[2,3] If applying the new criteria, physicians assign a diagnosis of PD to individuals meeting criteria regardless of cognitive status, with the option to qualify patients with the distinction "PD, dementia with Lewy bodies subtype."[2,3] The rationale for this change included overlapping prodromal, clinical, and pathologic findings between individuals diagnosed with PD, PD dementia, or DLB.

This change was met with dismay by members of the Lewy Body Dementia Association Scientific Advisory Council, who argued to maintain DLB as a distinct diagnostic entity for reasons including (1) patients with DLB may have little or no parkinsonism, (2) some clinical and pathologic differences exist between patients with DLB and those with PD/PD dementia, and (3) the maintenance of distinct diagnoses has value for driving research and educating the lay community.[4] Arguments were well reasoned on both sides,[4,5] and the new PD criteria and subsequently published updated DLB criteria[6] are both currently used in clinical and research settings. For the purposes of this article, the classic distinction separating DLB from PD dementia will be maintained for discussions of the two entities, with a shared treatment section at the end. The division between DLB and PD dementia is also present in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) classification system, in which neurocognitive disorder with Lewy bodies and neurocognitive disorder due to PD are separate diagnoses.[7]

DEMENTIA WITH LEWY BODIES

Revised clinical diagnostic criteria for DLB were published in 2017.[6] Major updates to the previous criteria included separation of clinical features and biomarkers, removal of the suggestive feature category, elevation of RBD to a core clinical feature based on interim evidence, and demotion of antipsychotic (neuroleptic) hypersensitivity to a supportive feature based on declining frequency in clinical practice. Probable DLB is diagnosed in the context of a dementia consistent with the DLB phenotype and either two or more core clinical features or the presence of one core clinical feature and at least one indicative

KEY POINTS

- **Lewy body dementia is an umbrella term that includes the clinical diagnoses of both Parkinson disease dementia and dementia with Lewy bodies.**
- **According to current diagnostic criteria from the Dementia With Lewy Bodies Consortium, probable dementia with Lewy bodies is diagnosed in the context of a dementia consistent with the dementia with Lewy bodies phenotype and either two or more core clinical features or the presence of one core clinical feature and at least one indicative biomarker.**

biomarker (TABLE 6-1). Possible DLB is diagnosed in the context of a dementia consistent with the DLB phenotype and either one core clinical feature or one or more indicative biomarkers.

Epidemiology

In a 2014 systematic review and meta-analysis, the incidence of DLB was 3.8% of new dementia diagnoses, with prevalence estimates suggesting that DLB accounts for 4.2% of dementia diagnoses in community settings and 7.5% of diagnoses in secondary care.[8] These numbers likely underestimate the true prevalence of DLB, as it is suggested that one in three cases may be missed[9] and misdiagnosis as AD is common.[9,10] Advances in DLB diagnostic criteria improve diagnosis,[8] but the impact of the newest criteria is not yet known.

TABLE 6-1

Fourth Consensus Criteria for the Clinical Diagnosis of Dementia With Lewy Bodies[a]

Required Criterion

- Dementia, often with early and prominent deficits in attention, executive function, and visuoperceptual ability; prominent or persistent memory impairment tends to occur with progression.

Probable Dementia With Lewy Bodies

- Presence of two or more core clinical features (with or without indicative biomarker)
- One core clinical feature plus at least one indicative biomarker

Possible Dementia With Lewy Bodies

- Presence of one core clinical feature (no indicative biomarker)
- Presence of one or more indicative biomarkers but no core clinical features

Core Clinical Features

- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations
- Rapid eye movement (REM) sleep behavior disorder (may precede other symptoms)
- Parkinsonism (defined as one or more spontaneous cardinal features: bradykinesia, rest tremor, rigidity)[b]

CONTINUED ON PAGE 131

Clinical Diagnosis

As with any presentation for cognitive impairment, a thorough history is critical in the diagnostic evaluation of patients who may have DLB. Clinicians should query the onset of symptoms, cognitive weaknesses (eg, visuoperceptual errors, short-term memory problems), pattern of progression, and functional limitations (CASE 6-1). As dementia is a required criterion for DLB, the history must establish that cognitive changes are impacting function sufficiently to meet the dementia threshold. Core and supportive features of DLB (TABLE 6-1) are largely ascertained through the history. Probing for evidence of cognitive fluctuations is particularly important. While supportive features do not have a role in formal diagnosis, the presence of symptoms such as postural instability, repeated falls, excessive daytime sleepiness, transient episodes of

CONTINUED FROM PAGE 130

Supportive Clinical Features

- Severe sensitivity to antipsychotic agents
- Postural instability
- Repeated falls
- Syncope or other transient episodes of unresponsiveness
- Severe autonomic dysfunction (eg, constipation, orthostatic hypotension, urinary incontinence)
- Hypersomnia/excessive daytime sleepiness
- Hyposmia
- Hallucinations in nonvisual modalities
- Systematized delusions
- Apathy, anxiety, and depression

Indicative Biomarkers

- Reduced basal ganglia dopamine transporter uptake (SPECT or PET)
- Abnormal (low uptake) iodine 123-MIBG myocardial scintigraphy
- Confirmation of REM sleep without atonia on polysomnography

Supportive Biomarkers

- Relative preservation of medial temporal lobe structures on CT/MRI
- Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity and/or the cingulate island sign on FDG-PET imaging
- Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range

CT = computed tomography; EEG = electroencephalogram; FDG-PET = fludeoxyglucose positron emission tomography; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

[a] Modified with permission from McKeith IG, et al, Neurology.[6] © 2017 The Authors.

[b] The parkinsonism in dementia with Lewy bodies occurs after or concurrent with dementia onset. If parkinsonism is the only core clinical feature and appears only in the context of severe dementia, dementia with Lewy bodies is less likely.

CASE 6-1

A 70-year-old woman presented with her husband and daughter because of cognitive symptoms. Her husband reported that the patient had worked as a librarian without any difficulties and retired 5 years earlier. Two years before this presentation, she fell, broke her hip, and required a surgical repair. She was delirious and experienced hallucinations postoperatively and required an extended hospitalization because of cognitive changes before transfer to rehabilitation. Her family felt that she never fully recovered after the fall and hospitalization. Her husband took over the family finances and started managing her medications, appointments, and most meal preparation. While her hallucinations lessened after hospital discharge, she continued to sometimes see children in the room with her when no one was there. She also described the sensation that someone was with her although the room was empty. She had good days and bad days cognitively. Her family reported that sometimes they saw her staring off into space and had to make an effort to get her attention.

On examination, her Montreal Cognitive Assessment (MoCA) score was 19/30, with points lost on trails (-1), cube drawing (-1), clock hands (-1), digits backward (-1), subtraction (-1), phonemic fluency (-1), abstraction (-1), delayed recall (-3, improving by 2 with cueing), and date (-1).

Her speech was soft. She had mild rigidity at the neck and in both arms and mild to moderate bradykinesia bilaterally with finger taps, opening and closing of the hands, pronation-supination arm movements, and heel taps. She walked slowly with decreased stride length and limited arm swing. She took 5 steps to maintain her balance on the pull test but did not require the examiner to catch her. An MRI of the brain revealed mild to moderate global atrophy and mild chronic ischemic changes.

COMMENT

This case describes a typical presentation of dementia with Lewy bodies (DLB). Research suggests that individuals who have experienced delirium have an increased risk of subsequent development of DLB. The MoCA is used for cognitive screening rather than diagnosis but is consistent with a diagnosis of dementia in this patient. Her weaknesses were particularly in executive function, visuospatial tasks, concentration, and memory retrieval, a pattern common in DLB. Particularly given her previous high functioning as a librarian, her decline and functional impairments are consistent with a diagnosis of dementia. She meets criteria for probable DLB given the dementia, fluctuating cognition, visual hallucinations, and parkinsonism. The transient episodes of decreased responsiveness are common in DLB and may be mistaken for seizures. It is uncertain whether the fall resulting in hospitalization 2 years earlier was related to an early symptom of her DLB or mechanical contributors.

unresponsiveness, and autonomic dysfunction are valuable in further supporting a suspicion of DLB.

Examination of an individual for whom DLB is in the differential diagnosis should include orthostatic vital signs to investigate autonomic dysfunction. Cognitive screening is typically performed with either the Montreal Cognitive Assessment (MoCA) or the Mini-Mental State Examination (MMSE). The MoCA is generally favored over the MMSE for screening in DLB given wider domain coverage (eg, more executive and visuospatial tasks) and fewer ceiling and floor effects.[11] Evaluation for parkinsonism includes observation for tremor, assessment of rigidity, bradykinesia testing, and evaluation of gait and postural stability. Myoclonus is sometimes seen in patients with DLB but is also observed in other dementia syndromes.

Diagnostic Evaluation

Diagnosis of DLB is possible based on the history and physical examination alone, but further testing can be helpful in establishing the diagnosis. Formal neuropsychological assessment can determine the severity of cognitive changes and the pattern of deficits, both of which help in the assessment of DLB. It is recommended that neuropsychological testing cover the full range of cognitive domains impacted in DLB, in which visual processing, attention, and executive functioning are typically more impaired than memory and naming.[6]

The updated criteria for DLB outline diagnostic evaluations serving as indirect biomarkers (TABLE 6-1).[6] Direct imaging of α-synuclein pathology is not yet available. The recommended studies are most helpful for patients in whom diagnostic uncertainty exists (CASE 6-2). Research suggests that dopamine transporter imaging can be helpful in clarifying the diagnosis in individuals identified as having possible DLB.[12] Low dopamine transporter uptake in the basal ganglia (FIGURE 6-1) is consistent with the presence of a parkinsonian syndrome but cannot be used to distinguish between parkinsonian conditions (eg, PD, DLB, multiple-system atrophy, progressive supranuclear palsy, and some cases of frontotemporal dementia). Thus, dopamine transporter imaging is most useful in differentiating DLB from conditions without usual parkinsonism, such as AD.

It is now established that patients formally diagnosed with idiopathic RBD have a markedly increased risk of developing a synuclein-related neurodegeneration, with over 75% of individuals with idiopathic RBD diagnosed with a neurodegenerative disease after 10 years of follow-up.[13] Whereas RBD is rarely associated with AD pathology, it is commonly associated with Lewy body disease, particularly if RBD preceded other neurodegenerative symptoms,[14] and individuals with a history of RBD are 6 times more likely to have autopsy-confirmed DLB than other neurodegenerative dementias.[15]

[^{123}I]Metaiodobenzylguanidine (MIBG) myocardial scintigraphy, where available, quantifies postganglionic sympathetic cardiac innervation, which is more likely to be reduced in Lewy body disease than in AD. Interpretation must occur in the context of medications that may impact testing (eg, tricyclic antidepressants and labetalol) and confounding diagnoses (eg, diabetes mellitus, peripheral neuropathies, and cardiac disease).[6]

Occipital hypometabolism on fludeoxyglucose positron emission tomography (FDG-PET) (FIGURE 6-2) correlates with the expected pathology in DLB, but it does not have sufficient sensitivity and specificity to qualify as an indicative

KEY POINTS

- In dementia with Lewy bodies, visual processing, attention, and executive functioning are typically more impaired than memory and naming.
- Individuals with a history of rapid eye movement sleep behavior disorder are 6 times more likely to have autopsy-confirmed dementia with Lewy bodies than other neurodegenerative dementias.

CASE 6-2

A 73-year-old man presented with memory complaints. His wife, who accompanied him, was frustrated that he never remembered what she asked him to do, such as take out the garbage or pick up certain items at the grocery store. He also frequently repeated the same questions. His family recently asked him to stop driving after he drove too close to a parked car and scraped the sides of both vehicles. He also drove a riding mower so close to a ledge on their property that it went over the ledge with just enough warning for him to scramble off. He was mildly slower than he used to be, but his wife thought this was similar to their friends of the same age. They had slept in separate beds for years because he kept her awake at night by yelling out in his sleep or hitting her while dreaming, a few times resulting in bruising.

On examination, his Montreal Cognitive Assessment (MoCA) score was 14/30, with points lost on trails (-1), cube drawing (-1), clock numbers and hands (-2), confrontation naming (-1, describing the rhinoceros as a hippopotamus), digits backward (-1), subtraction (-2), phonemic fluency (-1), abstraction (-2), delayed recall (-5, improving by 3 with cueing), and date (-1), with a point given for a 12th-grade educational level.

He had no rigidity on examiner assessment and minimal slowing with hand tasks. He had a mildly hunched posture and mildly slow gait speed but normal stride length and postural stability. Dopamine transporter single-photon emission computed tomography (SPECT) showed symmetrically decreased dopamine binding, consistent with a parkinsonian process.

COMMENT

By history, this patient had both amnestic and visuoperceptual concerns. While the amnestic symptoms prompted inclusion of Alzheimer disease in the differential diagnosis, the prominent visuospatial symptoms and the pattern of domain involvement on the MoCA suggested the possibility of an alternative diagnosis. The history suggested possible rapid eye movement (REM) sleep behavior disorder (RBD), particularly given the history of bed partner injury. Validated RBD screening questionnaires could be used to assess this further. RBD can occur years before other symptoms, suggesting a neurodegenerative process. Without a clear history of cognitive fluctuations or visual hallucinations or evidence of definite parkinsonism on examination, this patient met criteria for possible dementia with Lewy bodies (DLB). The positive dopamine transporter SPECT scan changed the diagnosis from possible to probable DLB. This is an example of how imaging can be used to increase diagnostic confidence. Polysomnographic confirmation of REM sleep without atonia would also change the diagnosis from possible to probable DLB, but it is currently unknown how relying on paired clinical features and biomarkers (ie, parkinsonism and reduced dopamine transporter uptake or clinical RBD and REM sleep without atonia on polysomnography) impact criteria performance. The fact that the patient met criteria for probable DLB did not exclude the possibility that he also had Alzheimer disease pathology, as the two diseases commonly co-occur.

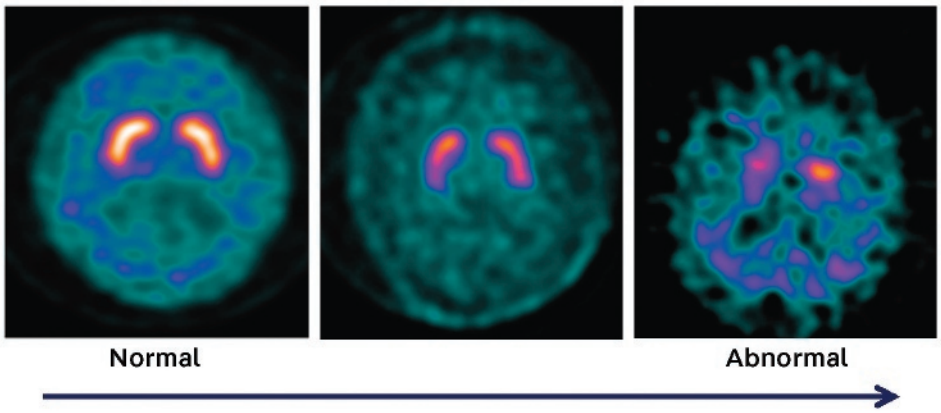

FIGURE 6-1
Dopamine transporter single-photon emission computed tomography (SPECT) images in parkinsonian syndromes. This series of dopamine transporter SPECT images shows a range of results ranging from normal to markedly abnormal. Tracer uptake is often symmetrically reduced in dementia with Lewy bodies, but this finding is also seen in other parkinsonian conditions.

biomarker.[6] The presence of the cingulate island sign on FDG-PET (reflecting relative preservation of posterior or midcingulate metabolism compared to surrounding structures) (FIGURE 6-2) is described in DLB, but research is ongoing regarding how to optimize accurate assessment.[6,16] Quantitative EEG demonstrating prominent posterior slow-wave activity with periodic fluctuations in the pre-alpha/theta range may also distinguish individuals with DLB from those with AD and thus is currently categorized in the supportive biomarker category.[6]

The final supportive biomarker is the finding of relative preservation of medial temporal lobe structures on either CT or MRI (FIGURE 6-3).[6] Atrophy of medial temporal lobe structures is common in AD, thus its absence is suggestive of an alternative diagnosis, such as DLB. It is notable, however, that the presence of medial temporal atrophy does not exclude the possibility of DLB. Mixed-pathology cases with AD and Lewy body changes are common. Clinically, individuals with probable DLB and a CSF biomarker profile consistent with AD have worse memory performance, more frequent hallucinations, and higher rates

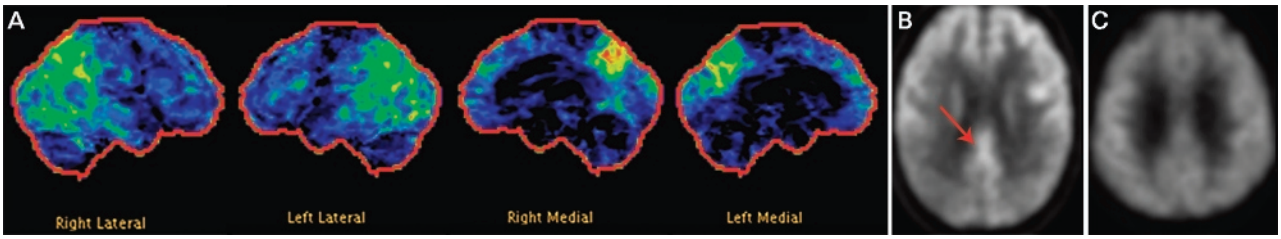

FIGURE 6-2
Fludeoxyglucose positron emission tomography (FDG-PET) findings in dementia with Lewy bodies (*z* score). *A*, Occipital and parietal hypometabolism demonstrated on the FDG-PET scans of patients with dementia with Lewy bodies. *B*, Axial FDG-PET images demonstrate the cingulate island sign (preservation of posterior cingulate metabolism relative to cuneus and precuneus) (*arrow*) in a patient with dementia with Lewy bodies and the absence of this finding in a patient with Alzheimer disease (*C*).

KEY POINTS

- Parkinson disease psychosis includes a broad range of experiences, including hallucinations in various modalities, sense of presence or passage, illusions, and delusions.
- The American Academy of Neurology Parkinson disease quality measurement set includes a measure identifying the percentage of patients with Parkinson disease who were assessed for cognitive dysfunction in the past 12 months using a recommended screening tool or neuropsychological assessment.

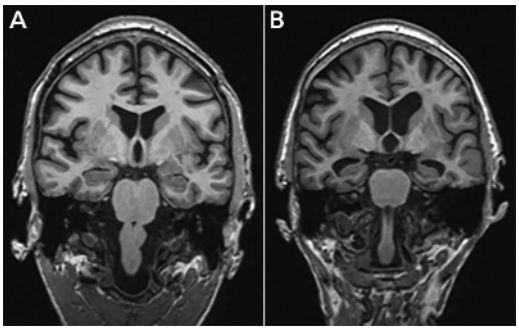

FIGURE 6-3
Coronal MRIs in dementia with Lewy bodies versus Alzheimer disease. Relative preservation of medial temporal lobe structures on T1-weighted imaging of a patient with dementia with Lewy bodies (*A*) in contrast to bilateral medial temporal lobe atrophy in a person with Alzheimer disease (*B*).

of nursing home placement and mortality than individuals who do not have such a CSF profile.[17] Pathologically, recent findings suggest that while the presence and severity of AD pathology may predict a faster disease course, α-synuclein burden is the primary driver, with a synergistic or additive effect from the concomitant tau and amyloid-β pathology.[18] Given these findings, AD biomarkers may play a future role for predicting prognosis for patients with DLB, but their presence cannot be used to exclude a DLB diagnosis.

PARKINSON DISEASE DEMENTIA

PD dementia is diagnosed in the context of an established diagnosis of PD and consists of identifying a profile of cognitive and behavioral changes consistent with PD and excluding other potential contributors (TABLE 6-2[19,20]). While the criteria for PD dementia highlight well-formed visual hallucinations (the most common hallucination type in PD dementia), PD psychosis includes a broad range of experiences, including hallucinations in various modalities, sense of presence or passage, illusions, and delusions (TABLE 6-3).[21] Presence hallucinations, passage hallucinations, and illusions are classified as "minor" hallucinatory phenomena and are common in patients with PD.[19] PD psychosis is associated with PD dementia but also occurs in patients with PD not meeting criteria for dementia, in whom it is a risk factor for subsequent PD dementia development.[22]

Epidemiology

The point prevalence of PD dementia is estimated to be around 25% to 30% of patients with PD.[22] Dementia frequency increases with disease duration and with age. Most individuals with PD have cognitive impairment by 15 years of disease duration, either PD dementia (48%) or mild cognitive impairment (MCI) (36%).[23] In individuals with PD surviving to 20 years of disease, the prevalence of PD dementia increases to 83%, with most individuals showing evidence of dementia before death.[24]

Clinical Diagnosis

The approach to diagnosing PD dementia is unique in that the epidemiologic data suggest that in the context of a PD diagnosis, the development of some degree of cognitive impairment is almost inevitable. Because of this, the American Academy of Neurology (AAN) PD quality measurement set includes a measure identifying the percentage of patients with PD who were assessed for cognitive dysfunction in the past 12 months using a recommended screening tool or neuropsychological assessment.[25] The measurement set details seven cognitive screening tools considered appropriate for use based on other assessments.

Criteria for the Diagnosis of Parkinson Disease Dementia[a]

TABLE 6-2

Core (Required) Features/Criteria (for Both Probable and Possible Parkinson Disease Dementia)

- Parkinson disease diagnosis (according to Queen Square Brain Bank criteria[20])
- Dementia developing within context of established Parkinson disease with impairment in more than one cognitive domain[b]

Probable Parkinson Disease Dementia

- Typical cognitive profile with impairment in at least two of four cognitive domains: attention, executive function, visuospatial reasoning, and memory (usually improves with cueing)
- Presence of at least one supportive behavioral feature
- No features to suggest alternative pathology (eg, probable vascular dementia, delirium due to systemic disease or drug intoxication, major depression)
- No features that make the diagnosis less certain (timing of motor and cognitive symptoms unknown, abnormality that could impact cognition even if not suspected to be cause of dementia, [eg, vascular changes on imaging])

Possible Parkinson Disease Dementia

- Atypical cognitive profile in one or more domains (eg, prominent fluent aphasia, memory deficits not improving with cueing)
- Behavioral symptoms may or may not be present
- No features to suggest alternative pathology (eg, probable vascular dementia, delirium due to systemic disease or drug intoxication, major depression)

Cognitive Features

- Impaired attention +/– fluctuations
- Impaired executive function, bradyphrenia
- Impaired visuospatial function
- Memory: impaired free recall of recent events and learning new material, usually improving with cueing; recognition typically better than free recall
- Language: largely preserved, but word-finding difficulties and impaired complex sentence comprehension may be present

Behavioral Features

- Apathy
- Depression, anxiety
- Hallucinations (usually visual and consisting of complex, formed visions of people, animals, or objects)
- Delusions (usually paranoid)
- Excessive daytime sleepiness

[a] Modified with permission from Emre M, et al, Mov Disord.[19] © 2007 Movement Disorder Society.
[b] As with dementia in general, cognitive changes should represent a change from baseline, have insidious onset and gradual progression, and be associated with functional impairment relating to cognition (not motor or autonomic symptoms).

A more recent International Parkinson and Movement Disorder Society task force identified only three global screening scales recommended without caveats for use in PD: the MoCA, Dementia Rating Scale-Second Edition (DRS-2), and Parkinson's Disease-Cognitive Rating Scale (PD-CRS).[26]

Parkinson Disease Mild Cognitive Impairment

With routine screening of individuals with PD by querying for subjective cognitive complaints and performing formal cognitive screening assessments, clinicians will identify individuals with PD demonstrating a range of cognitive dysfunction. The concept of MCI, initially proposed in the context of individuals with amnestic concerns, was later also defined within the context of PD. Formal diagnostic criteria for PD-MCI were published in 2012 (TABLE 6-4).[27] As with MCI in other contexts, individuals with PD-MCI can progress, remain stable, or revert to normal cognition.[22] Individuals with PD-MCI have an increased risk of progression to PD dementia,[22,28] although estimated conversion rates vary by cohort (eg, relating to age, disease duration) and criteria used. Given the expected progression of PD to include dementia over time, PD-MCI likely reflects a transitional state for many individuals meeting criteria (CASE 6-3), but its role in predicting the trajectory for individual patients requires further study. The diagnosis of PD-MCI should prompt clinicians to identify potentially modifiable risk factors for cognitive impairment (eg, sleep apnea, medication effects), perform serial evaluations to monitor for changes in cognitive status, assess functional capabilities, and counsel patients and families to discuss long-term planning topics (eg, advance directives, driving safety, finances, and estate planning). These approaches reflect recommendations from the AAN MCI guideline update[29] (SDC APPENDIX, *links.lww.com/CONT/A261*) that also have relevance within the context of PD-MCI.

Diagnostic Evaluation

If individuals have established PD and develop dementia in a pattern consistent with PD dementia, additional testing may not be required. Neuropsychological

TABLE 6-3 **Types of Psychosis in Parkinson Disease**

Hallucination

- Abnormal perception without a physical stimulus
- Can occur in any sensory modality (visual, auditory, tactile, olfactory, gustatory)
- May be simple or complex

Sense of Presence

- Experience that someone is present when no one is actually there

Sense of Passage

- Fleeting, vague images in one's peripheral vision

Illusion

- Misperceptions of real stimuli (often visual)

Delusion

- False, fixed, idiosyncratic belief that is maintained despite evidence to the contrary

testing can be helpful to establish a baseline, investigate cognitive impairment in individuals in whom screening may be less accurate (eg, in the context of either high or low educational attainment), or answer specific clinical questions (eg, pertaining to risk for deep brain stimulation or assessing atypical features). If atypical features are seen in the history, examination, or neuropsychological testing, the workup can include evaluations for overlapping processes, such as structural MRI to investigate the degree of vascular burden or the appearance of medial temporal lobe structures. Comorbid pathology is common in Lewy body diseases, with recent research demonstrating that most individuals with Lewy body dementia (both DLB and PD dementia) had two or three concomitant pathologies, particularly AD.[30] Thus, similar to DLB, diagnostic testing results consistent with AD or other diagnoses do not exclude PD dementia but rather suggest comorbid diseases.

NATURAL HISTORY

While the clinical and pathologic features of DLB and PD dementia overlap, the presentation and course are commonly different. In individuals with DLB, parkinsonian symptoms develop on average 2 years after the onset of dementia.[15] Motor symptoms are often milder in DLB than in PD but may respond less well to medication. Median survival of patients with clinically diagnosed DLB was only 3.72 years (95% confidence interval, 3.33 to 4.14) in a 2017 naturalistic cohort.[31] This is in contrast to individuals with PD dementia, who had PD symptoms for an average of 10.9 (standard deviation 5.5) years before dementia in the Sydney Multicenter Study.[24] Given the longer disease duration and motor progression, individuals with PD dementia have greater motor disability, more frequent motor fluctuations, higher medication burden, and more invasive treatment histories (eg, deep brain stimulation) than those with DLB. After PD dementia diagnosis, median survival in the Sydney Multicenter Study was 54 months.[24] The few studies examining cause of death in Lewy body dementia combine DLB and PD dementia. In a 2016 study, dementia was described as a contributor to death 71% of the time, followed by circulatory (45%) and respiratory (38%) contributors,[32] consistent with reports that pneumonia is the most common cause of death in PD dementia (25%).[24]

Criteria for the Diagnosis of Parkinson Disease Mild Cognitive Impairment[a] TABLE 6-4

- Parkinson disease diagnosis (according to United Kingdom Brain Bank criteria[20])
- Gradual cognitive decline either described by subjective report from the patient or informant or observed by the clinician
- Cognitive impairment based on testing[b]
- No functional impairment relating to cognition (subtle difficulties on complex tasks permitted)
- No other explanation for the cognitive decline (eg, delirium, major depression)

[a] Data from Litvan I, et al, Mov Disord.[27]

[b] Testing should reflect cognitive performance and not comorbidities such as motor impairment or severe anxiety. Patients can be diagnosed as Parkinson disease mild cognitive impairment (PD-MCI) Level I based on an abbreviated or screening assessment or PD-MCI Level II based on a comprehensive neuropsychological assessment. Formal criteria for these designations are provided in the published criteria.

CASE 6-3

A 68-year-old man with a 10-year history of Parkinson disease (PD) presented for a follow-up visit. He was a successful trial lawyer at the time of PD diagnosis, but when he was 64 years of age, he reported increasing difficulty in the courtroom. He described having trouble giving closing statements spontaneously and an increased reliance on notes. His Montreal Cognitive Assessment (MoCA) at that time was 27/30, with points lost for a subtle error on cube copying, the phonemic fluency task, and delayed recall (improving with cueing). He retired 1 year later because of a combination of these difficulties, moderate dysarthria, and motor fluctuations making the timing of court appearances more challenging.

At this follow-up visit, he reported difficulty reading books because he could not keep track of the plots. His wife had taken over the family finances after noticing that it was taking him longer to balance the checkbook and that he had paid a large bill twice. She also noticed that he was no longer able to fix things around the house; he would take electronic things apart and forget how to put them back together. Along with these changes, he was sleeping more during the day and appeared increasingly depressed. Neuropsychological testing showed significant declines in attention, executive, and memory retrieval tasks compared to estimated premorbid levels.

COMMENT

It is likely that this patient had PD mild cognitive impairment (PD-MCI) at the age of 64 when he noticed an impact of cognitive changes at work. If his MoCA score of 27/30 is considered sufficient for screening positive for cognitive impairment using an abbreviated scale, he met criteria for PD-MCI level I. The commonly recommended cutoff for cognitive impairment on the MoCA is 26, but recommended cutoffs in PD vary. Given his high-functioning baseline and the fact that the points lost were consistent with the domains typically involved in PD-MCI, the MoCA was probably capturing true early cognitive impairment. The subsequent progression of cognitive decline and increasing functional impairments suggested the later development of dementia, further supported by the neuropsychological testing results and development of behavioral features. The etiology of behavioral changes in PD and PD-related cognitive impairment is often multifactorial, reflecting both neurochemical changes and "reactive" considerations in which patients sleep more because of trouble concentrating on tasks and become depressed because of decreasing functional abilities.

TREATMENT

Treatment for Lewy body dementia is currently symptomatic only. Strategies for treating DLB and PD dementia thus overlap, although no medications are approved by the US Food and Drug Administration (FDA) specifically for the treatment of DLB. As described in the AAN dementia management measurement set update,[33] treating individuals with Lewy body dementia and their families should include querying safety concerns and driving safety, assessing pain, screening for and managing behavioral and psychiatric symptoms, discussing pharmacologic and nonpharmacologic treatment approaches, encouraging advance care planning, and providing palliative care counseling and caregiver education and support.

Pharmacologic Approaches

The first step in successfully treating an individual with Lewy body dementia is to identify medications the patient is taking that could contribute to symptoms or are best avoided in older adults with dementia. This includes benzodiazepines, anticholinergic/antimuscarinic medications (eg, for genitourinary symptoms), antipsychotic drugs, and tricyclic antidepressants.[34] Antipsychotic use is of particular concern in individuals with DLB given the risk of hypersensitivity reactions (eg, sudden deterioration, severe parkinsonism, and mental status changes ranging from worsened confusion to unresponsiveness). Appropriate prescribing of this medication class is discussed further below. Particularly in the context of PD dementia, the potential contribution of antiparkinsonian medications should be assessed. Anticholinergic medications used to treat tremor (eg, trihexyphenidyl, benztropine), dopamine agonists, and amantadine are associated with worsened cognition and psychosis. Gradual cessation of these medications can result in cognitive-behavioral improvement.

Cognitive symptoms in Lewy body dementia are treated with cholinesterase inhibitors, with use supported by multiple systematic reviews and meta-analyses.[35,36] Rivastigmine is the only cholinesterase inhibitor FDA approved for use in PD dementia (TABLE 6-5). While not systematically reported in the literature, a dramatic response to initiation of cholinesterase inhibitors in a subset of individuals with Lewy body dementia is observed in clinical settings. Gastrointestinal symptoms are the most common adverse event, but cholinesterase inhibitors can also worsen tremor in individuals with parkinsonism. Less evidence exists for memantine efficacy in Lewy body dementia, but it is generally well tolerated and may be used either as single or adjunctive therapy.[6,35,36]

Behavioral symptoms observed in individuals with Lewy body dementia include psychosis, depression, anxiety, and apathy. Evidence suggests that cholinesterase inhibitors improve behavioral symptoms for some patients.[35,36] Using these agents to address multiple symptoms can be a prudent initial approach. Nonbothersome hallucinations and delusions may not require treatment. Pimavanserin was approved by the FDA for PD psychosis in 2016 based on a single randomized controlled trial,[37] and it is the only approved treatment for this indication (TABLE 6-5). FDA labeling includes a boxed warning stating, "Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death" and cautioning that pimavanserin is only approved for hallucinations and delusions associated with PD psychosis.[38] An additional warning cautions to avoid use if patients have risk factors (including use of other drugs) for prolonged QT interval. While

KEY POINTS

- The diagnosis of Parkinson disease-mild cognitive impairment should prompt clinicians to identify potentially modifiable risk factors for cognitive impairment, perform serial evaluations to monitor for changes in cognitive status, assess functional capabilities, and counsel patients and families to discuss long-term planning topics.
- In a 2016 study examining cause of death in Lewy body dementia, dementia was described as a contributor to death 71% of the time, followed by circulatory (45%) and respiratory (38%) contributors, consistent with reports that pneumonia is the most common cause of death in Parkinson disease dementia (25%).
- Treating individuals with Lewy body dementia and their families should include querying safety concerns and driving safety, assessing pain, screening for and managing behavioral and psychiatric symptoms, discussing pharmacologic and nonpharmacologic treatment approaches, encouraging advance care planning, and providing palliative care counseling and caregiver education and support.
- The first step in successfully treating an individual with Lewy body dementia is to identify medications that could contribute to symptoms or are best avoided in older adults with dementia.

TABLE 6-5 **Medications Commonly Used for Cognition and Psychosis in Lewy Body Dementia**

Indication/Drug	FDA Approved?[a]	Dose	Common Adverse Events[b]
Cognition			
Rivastigmine patch	Yes	4.6 mg, 9.5 mg, or 13.3 mg patch per 24 hours (transdermal)	Gastrointestinal (decreased appetite, diarrhea, nausea, vomiting), urinary tract infections, falls
Rivastigmine oral	Yes	1.5 mg, 3 mg, 4.5 mg, or 6 mg 2 times a day (oral)	Endocrine (weight loss), gastrointestinal (abdominal pain, diarrhea, indigestion, loss of appetite, nausea, vomiting), neurologic (asthenia, dizziness, headache, tremor)
Donepezil	No	5 mg or 10 mg in the morning (oral)	Cardiovascular (hypertension, syncope), endocrine (weight loss), hematologic (contusion, ecchymosis), musculoskeletal (cramps, increased creatine kinase level), neurologic (asthenia, dizziness, headache, insomnia, somnolence), psychiatric (depression, dream disorder), renal (urinary incontinence), other (fatigue)
Galantamine	No	4 mg, 8 mg, or 12 mg 2 times a day (oral)	Gastrointestinal (decreased appetite, diarrhea, nausea, vomiting), neurologic (dizziness, headache)
Memantine	No	Immediate release: 5 mg or 10 mg tablets, titrating to 10 mg 2 times a day (oral) Extended release: 7 mg, 14 mg, 21 mg, or 28 mg once a day (oral)	Gastrointestinal (constipation, diarrhea, vomiting), neurologic (confusion, dizziness, headache)
Psychosis			
Pimavanserin[c]	Yes	17 mg or 34 mg once daily (oral)	Cardiovascular (peripheral edema), gastrointestinal (nausea), neurologic (confusional state)
Clozapine[c,d]	No	Typical dosing 6.25–50 mg nightly (oral)	Cardiovascular (hypotension, syncope, tachycardia), endocrine (sweating, weight gain), gastrointestinal (constipation, excessive salivation, nausea, xerostomia), neurologic (dizziness, headache, sedation, somnolence, tremor, vertigo), ophthalmic (visual disturbance), other (fever)
Quetiapine[c]	No	Regular-release typical dosing: 25–150 mg once daily (oral)	Cardiovascular (orthostatic hypotension, tachycardia), endocrine (increased serum cholesterol and triglycerides, weight gain), gastrointestinal (abdominal pain, constipation, increased appetite, indigestion, xerostomia), hepatic (increased liver enzymes), musculoskeletal (backache), neurologic (asthenia, dizziness, extrapyramidal symptoms, headache, insomnia, lethargy, somnolence, tremor), psychiatric (agitation), respiratory (nasal congestion, pharyngitis), other (fatigue, pain)

FDA = US Food and Drug Administration.
[a] For use in Parkinson disease; no drug is FDA approved for use in dementia with Lewy bodies.
[b] Adverse effects in adult populations as reported in Micromedex (accessed 1/29/2018).
[c] All antipsychotic agents have a boxed warning regarding increased risk of death in patients with dementia-related psychosis.
[d] Available only under a restricted distribution program (the Clozapine Risk Evaluation and Mitigation Strategy [REMS] Program) through which blood counts are monitored given risk of agranulocytosis.

high-level efficacy data are lacking,[36] quetiapine and clozapine are also commonly used to treat psychosis in the context of PD and Lewy body dementia as these are safer than alternative antipsychotics. Clozapine has a higher level of evidence for use for PD psychosis than quetiapine but requires regular blood count monitoring for evidence of agranulocytosis.[39] Quetiapine is simpler to prescribe but is associated with increased mortality in individuals with PD.[40] In rare cases, clinicians, patients, and families may be forced to consider antipsychotics with a riskier safety profile given psychosis severity and lack of response to other strategies. In these circumstances, shared decision making takes on an increasingly important role as potential risks and benefits are weighed.[41] All antipsychotic agents have a boxed warning regarding increased risk of death in patients with dementia-related psychosis. High-level evidence for specific agents for the treatment of depression, anxiety, and apathy in Lewy body dementia is lacking,[36] and treatment usually follows best practices for the treatment of these conditions in older adults in general.

Treatment of motor symptoms in Lewy body dementia is largely achieved through levodopa preparation monotherapy given the risks of exacerbating cognitive-behavioral symptoms with other antiparkinsonian medications. Some parkinsonian motor features, such as gait and balance dysfunction, are usually unresponsive to levodopa and are best treated with nonpharmacologic approaches.

A myriad of other symptoms in Lewy body dementia can benefit from pharmacologic treatment, including RBD, orthostasis, constipation, and sialorrhea. Melatonin is the first-line treatment for RBD in the context of Lewy body dementia, but clonazepam is often cautiously tried if melatonin is not sufficiently helpful.[42] Orthostatic hypotension is addressed by weaning contributing medications (eg, dopamine agonists and antihypertensive treatment, if able), nonpharmacologic strategies, and prescription approaches (eg, midodrine, fludrocortisone, droxidopa). Constipation is treated with increased water intake, dietary changes, and various over-the-counter and prescription therapies not specific to PD. Sialorrhea is treated with botulinum toxin injections, glycopyrrolate, ipratropium bromide sublingual spray, and atropine sublingual drops.[43] Pharmacologic interventions are guided by the symptoms most prominently impacting quality of life, with patients and caregivers weighing the potential benefits and risks.

Nonpharmacologic Approaches

Nonpharmacologic approaches are an important aspect of treating individuals with Lewy body dementia. While few studies have investigated the impact of exercise for individuals with Lewy body dementia,[44] exercise and physical activity are recommended in this context given increasing evidence of benefit for individuals with PD, including long-term benefits.[45] Physical therapy, occupational therapy, and speech-language pathology assessments (addressing both speech and swallowing) are also important interdisciplinary considerations for care. Therapy sessions will usually include both patients and caregivers to compensate for cognitive limitations of patients and to teach caregiver-specific skills (eg, assistance in transfers and fall reduction). Swallow assessments are critical given that respiratory causes of death are common in Lewy body dementia.[24,32] Connecting patients and caregivers to social work resources helps identify strategies to reduce caregiver burden. Dementia is a contributor to the

KEY POINTS

- **Cognitive symptoms in Lewy body dementia are treated with cholinesterase inhibitors, with use supported by multiple systematic reviews and meta-analyses.**
- **Pimavanserin was approved by the US Food and Drug Administration for Parkinson disease psychosis in 2016 based on a single randomized controlled trial, and it is the only approved treatment for this indication. While high-level efficacy data are lacking, quetiapine and clozapine are also commonly used to treat psychosis in the context of Parkinson disease and Lewy body dementia as these are safer than alternative antipsychotics. All antipsychotic agents have a boxed warning regarding increased risk of death in patients with dementia-related psychosis.**
- **Melatonin is first-line treatment for rapid eye movement sleep behavior disorder in the context of Lewy body dementia, but clonazepam is often cautiously tried if melatonin is not sufficiently helpful.**
- **Physical therapy, occupational therapy, and speech-language pathology assessments (addressing both speech and swallowing) are important interdisciplinary considerations for care of patients with Lewy body dementia. Therapy sessions will usually include both patients and caregivers to compensate for patients' cognitive limitations and also to teach caregiver-specific skills (eg, assistance in transfers and fall reduction).**

cause of death for most individuals diagnosed with Lewy body dementia,[32] and palliative care and hospice approaches are a critical component of quality care.[33]

TRENDS

It is likely that debates regarding the PD, PD dementia, and DLB diagnostic categories will continue in the short term. Shifting to pathologic categorization (eg, Lewy body disease-dementia, Lewy body disease-parkinsonism) has been proposed and may become particularly relevant if α-synuclein biomarkers are identified. Efforts are under way to identify both PD[46] and DLB[47] prodromal states, efforts that will inevitably emphasize the overlap between the two conditions. The focus on α-synuclein pathology has both therapeutic and diagnostic implications as phase 2 studies testing anti–α-synuclein antibodies are now enrolling for the treatment of PD.[48,49]

CONCLUSION

DLB and PD dementia have overlapping clinical and pathologic features, but the timing of symptom onset and related disease challenges result in differences in counseling and approach. Diagnosis is determined based on history, clinical examination, and supportive diagnostic testing, if indicated, although identification of comorbid pathology cannot exclude a Lewy body diagnosis. The high prevalence of cognitive impairment with the progression of PD means that individuals with PD should be regularly screened for cognitive changes and educated regarding what to expect. Treatment is currently symptomatic and consists of avoiding medications that may cause or exacerbate symptoms; pharmacologic agents to address bothersome symptoms impacting quality of life; exercise and physical, occupational, and speech-language therapy; education and counseling; caregiver support; and palliative care referrals. Areas of active research include defining prodromal states, refining diagnostic accuracy, identifying biomarkers, developing disease-modifying therapies, and improving end-of-life care.

USEFUL WEBSITES

LEWY BODY DEMENTIA ASSOCIATION
The Lewy Body Dementia Association provides educational resources for medical professionals, patients, and families regarding the diagnosis and treatment of Lewy body dementia; links caregivers to online and local support; and highlights Lewy body dementia research opportunities.
lbda.org

REFERENCES

1 Barker WW, Luis CA, Kashuba A, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the state of Florida Brain Bank. Alzheimer Dis Assoc Disord 2002;16(4):203–212. doi:10.1097/00002093-200210000-00001.

2 Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30(12):1591–1601. doi:10.1002/mds.26424.

3 Berg D, Postuma RB, Bloem B, et al. Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. Mov Disord 2014;29(4):454–462. doi:10.1002/mds.25844.

4 Boeve BF, Dickson DW, Duda JE, et al. Arguing against the proposed definition changes of PD. Mov Disord 2016;31(11):1619–1622. doi:10.1002/mds.26721.

5 Postuma RB, Berg D, Stern M, et al. Abolishing the 1-year rule: how much evidence will be enough? Mov Disord 2016;31(11):1623–1627. doi:10.1002/mds.26796.

6 McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology 2017;89(1):88–100. doi:10.1212/WNL.0000000000004058.

7 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed (DSM-5). Washington, D C: American Psychiatric Association, 2013.

8 Vann Jones SA, O'Brien JT. The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. Psychol Med 2014;44(4):673–683. doi:10.1017/S0033291713000494.

9 Thomas AJ, Taylor JP, McKeith I, et al. Development of assessment toolkits for improving the diagnosis of the Lewy body dementias: feasibility study within the DIAMOND Lewy study. Int J Geriatr Psychiatry 2017;32(12): 1280–1304. doi:10.1002/gps.4609.

10 Galvin JE, Duda JE, Kaufer DI, et al. Lewy body dementia: the caregiver experience of clinical care. Parkinsonism Relat Disord 2010;16(6): 388–392. doi:10.1016/j.parkreldis.2010.03.007.

11 Biundo R, Weis L, Bostantjopoulou S, et al. MMSE and MoCA in Parkinson's disease and dementia with Lewy bodies: a multicenter 1-year follow-up study. J Neural Transm (Vienna) 2016;123(4): 431–438. doi:10.1007/s00702-016-1517-6.

12 Walker Z, Moreno E, Thomas A, et al. Clinical usefulness of dopamine transporter SPECT imaging with 123I-FP-CIT in patients with possible dementia with Lewy bodies: randomised study. Br J Psychiatry 2015;206(2):145–152. doi:10.1192/bjp.bp.114.148643.

13 Iranzo A, Fernández-Arcos A, Tolosa E, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One 2014;9(2):e89741. doi:10.1371/journal.pone.0089741.

14 Boeve BF, Silber MH, Ferman TJ, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. Sleep Med 2013;14(8):754–762. doi:10.1016/j.sleep.2012.10.015.

15 Ferman TJ, Boeve BF, Smith GE, et al. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. Neurology 2011; 77(9):875–882. doi:10.1212/WNL.0b013e31822c9148.

16 Imabayashi E, Soma T, Sone D, et al. Validation of the cingulate island sign with optimized ratios for discriminating dementia with Lewy bodies from Alzheimer's disease using brain perfusion SPECT. Ann Nucl Med 2017;31(7):536–543. doi:10.1007/s12149-017-1181-4.

17 Lemstra AW, de Beer MH, Teunissen CE, et al. Concomitant AD pathology affects clinical manifestation and survival in dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2017;88(2): 113–118. doi:10.1136/jnnp-2016-313775.

18 Ferman TJ, Aoki N, Crook JE, et al. The limbic and neocortical contribution of α-synuclein, tau, and amyloid β to disease duration in dementia with Lewy bodies. Alzheimers Dement 2018;14(3): 330–339. doi:10.1016/j.jalz.2017.09.014.

19 Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22(12): 1689–1707. doi:10.1002/mds.21507.507.

20 Hughes AF, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55(3): 181–184. doi:10.1136/jnnp.55.3.181.

21 Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. Mov Disord 2007;22(8):1061–1068. doi:10.1002/mds.21382.

22 Aarsland D, Creese B, Politis M, et al. Cognitive decline in Parkinson disease. Nat Rev Neurol 2017;13(4):217–231. doi:10.1038/nrneurol.2017.27.

23 Hely MA, Morris JG, Reid WG, Trafficante R. Sydney multicenter study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord 2005;20(2):190–199. doi:10.1002/mds.20324.

24 Hely MA, Reid WG, Adena MA, et al. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord 2008;23(6):837–844. doi:10.1002/mds.21956.

25 Factor SA, Bennett A, Hohler AD, et al. Quality improvement in neurology: Parkinson disease update quality measurement set: executive summary. Neurology 2016;86(24):2278–2283. doi:10.1212/WNL.0000000000002670.

26 Skorvanek M, Goldman JG, Jahanshahi M, et al. Global scales for cognitive screening in Parkinson's disease: critique and recommendations. Mov Disord 2018;33(2):208–218. doi:10.1002/mds.27233.

27 Litvan I, Goldman JG, Tröster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012;27(2): 349–356. doi:10.1002/mds.24893.

28 Hoogland J, Boel JA, de Bie RMA, et al. Mild cognitive impairment as a risk factor for Parkinson's disease dementia. Mov Disord 2017; 32(7):1056–1065. doi:10.1002/mds.27002.

29 Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018;90(3):126–135. doi:10.1212/WNL.0000000000004826.

30 Colom-Cadena M, Grau-Rivera O, Planellas L, et al. Regional overlap of pathologies in Lewy body disorders. J Neuropathol Exp Neurol 2017; 76(3):216–224. doi:10.1093/jnen/nlx002.

31 Price A, Farooq R, Yuan JM, et al. Mortality in dementia with Lewy bodies compared with Alzheimer's dementia: a retrospective naturalistic cohort study. BMJ Open 2017;7(11):e017504. doi:10.1136/bmjopen-2017-017504.

32 Garcia-Ptacek S, Kåreholt I, Cermakova P, et al. Causes of death according to death certificates in individuals with dementia: a cohort from the Swedish Dementia Registry. J Am Geriatr Soc 2016;64(11):e137–e142. doi:10.1111/jgs.14421.

33 Sanders AE, Nininger J, Absher J, et al. Quality improvement in neurology: dementia management quality measurement set update. Neurology 2017;88(20):1951–1957. doi:10.1212/WNL.0000000000003917.

34 O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 2015;44(2):213–218. doi:10.1093/ageing/afu145.

35 Wang HF, Yu JT, Tang SW, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. J Neurol Neurosurg Psychiatry 2015;86(2):135–143. doi:10.1136/jnnp-2014-307659.

36 Stinton C, McKeith I, Taylor JP, et al. Pharmacological management of Lewy body dementia: a systematic review and meta-analysis. Am J Psychiatry 2015; 172(8):731–742. doi:10.1176/appi.ajp.2015.14121582.

37 Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. [Erratum appears in Lancet 2014 Jul 5;384(9937): 28]. Lancet 2014;383(9916):533–540. doi:10.1016/S0140-6736(13)62106-6.

38 NUPLAZID (pimavanserin) prescribing information. *accessdata.fda.gov/drugsatfda_docs/label/2016/207318lbl.pdf*. Revised April 2016. Accessed November 30, 2018.

39 Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease. Mov Disord 2011;26(suppl 3):S42–S80. doi:10.1002/mds.23884.

40 Weintraub D, Chiang C, Kim HM, et al. Association of antipsychotic use with mortality risk in Patients with Parkinson disease. JAMA Neurol 2016;73(5): 535–541. doi:10.1001/jamaneurol.2016.0031.

41 Armstrong MJ, Weintraub D. The case for antipsychotics in dementia with Lewy bodies. Mov Disord Clin Pract 2017;4:32–35. doi:10.1002/mdc3.12383.

42 Howell MJ, Schenck CH. Rapid eye movement sleep behavior disorder and neurodegenerative disease. JAMA Neurol 2015;72(6):707–712. doi:10.1001/jamaneurol.2014.4563.

43 Srivanitchapoom P, Pandey S, Hallett M. Drooling in Parkinson's disease: a review. Parkinsonism Relat Disord 2014;20(11):1109–1118. doi:10.1016/j.parkreldis.2014.08.013.

44 Inskip M, Mavros Y, Sachdev PS, Fiatarone Singh MA. Exercise for individuals with Lewy body dementia: a systematic review. PLoS ONE 2016; 11(6):e0156520. doi:10.1371/journal.pone.0156520.

45 Mak MK, Wong-Yu IS, Shen X, Chung CL. Long-term effects of exercise and physical therapy in people with Parkinson disease. Nat Rev Neurol 2017;13(11): 689–703. doi:10.1038/nrneurol.2017.128.

46 Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord 2015;30(12):1600–1611. doi:10.1002/mds.26431.

47 McKeith I, Taylor JP, Thomas A, et al. Revisiting DLB diagnosis: a consideration of prodromal DLB and of the diagnostic overlap with Alzheimer disease. J Geriatr Psychiatry Neurol 2016;29(5): 249–253. doi:10.1177/0891988716656083.

48 ClinicalTrials.gov. Evaluating the safety, pharmacokinetics, and pharmacodynamics of BIIB054 in participants with Parkinson's disease (SPARK). *clinicaltrials.gov/ct2/show/NCT03318523?cond=NCT03318523+%E2%80%93+BIIB-054&rank=1*. Accessed November 30, 2018.

49 ClinicalTrials.gov. A study to evaluate the efficacy of prasinezumab (RO704615/PRX002) in participants with early Parkinson's disease (PASADENA). *clinicaltrials.gov/ct2/show/NCT03100149?cond=NCT03100149+%E2%80%93+PRX002%2FRO7046015&rank=1*. Accessed November 30, 2018.

DISCLOSURE

Continued from page 128

Dr Armstrong receives research/grant support from the Agency for Healthcare Research and Quality (K08HS24159), 1Florida Alzheimer's Disease Research Center (AG047266), and the Lewy Body Dementia Association Research Center of Excellence program and receives publishing royalties from Oxford University Press.