Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia, affecting about 1.5 million people in the United States, but it is underrecognized and often mismanaged in clinical practice. A delayed or nonspecific diagnosis adds to the burden that individuals with DLB and their caregivers experience, and increases the risk of lack of treatment or inappropriate medication use. This review aims to provide practicing neurologists with a comprehensive overview of DLB, encompassing its clinical presentation, diagnostic criteria, and management strategies. Through a thorough exploration of the latest research findings and clinical insights, this article aims to equip neurologists with the knowledge and tools necessary to navigate the complexities of DLB, ultimately enhancing care and outcomes.

**Diagnostic Criteria and Tools**

Diagnostic criteria for a clinical diagnosis of DLB were revised by the DLB Consortium and published in their fourth consensus report in 2017 (Table 1). These criteria have high specificity, but until recently there was no consensus on standard methods to assess signs and symptoms to improve the sensitivity of a DLB diagnosis. However, there are now several tools or sets of instruments that can be used to assess DLB signs and symptoms in a standardized fashion. One of the first was the Lewy Body Composite Score, which includes 5 motor signs of parkinsonism determined by an experienced provider and 6 nonmotor symptoms elicited from an informant. In people with mild cognitive impairment (MCI) or dementia, this scale showed good discriminating abilities when differentiating DLB from Alzheimer disease (AD) and MCI-DLB from MCI-AD. A quality-of-care research program—Improving the Diagnosis and Management of Neurodegenerative Dementia of Lewy Body Type (DIAMOND-Lewy)—developed an assessment toolkit (https://research.ncl.ac.uk/diamondlewy) based on the revised diagnostic criteria to improve diagnostic accuracy (Table 2). The National Institute on Aging Alzheimer’s Disease Research Center program added a Lewy body dementia module (LBD-MOD) to the Uniform Data Set to facilitate LBD characterization and diagnosis. The LBD-MOD includes 5 informant-based scales measuring autonomic symptoms, cognitive fluctuations, sleep symptoms and disorders, and neuropsychiatric symptoms, including visual hallucinations. Motor signs of parkinsonism are measured with the original Unified Parkinson’s Disease Rating Scale (UPDRS) part III. The LBD-MOD includes a novel test of visual misinterpretation (the Noise Pareidolia test).

**Evidence-Based and Expert-Opinion Treatment Recommendations**

As part of the DIAMOND-Lewy program, an evidence-based review of treatment options for DLB was completed. The findings from this review and expert opinion recommendations were combined into a detailed management toolkit (https://research.ncl.ac.uk/diamondlewy) for clinicians treating individuals with DLB.

**Clinical Features of DLB**

**Cognitive Symptoms**

Signs and symptoms of cognitive decline are required for a
diagnosis of DLB. Memory loss complaints are common, but information from the history, screening cognitive tests, and formal neuropsychological testing shows a unique pattern of cognitive deficits associated with DLB. When compared with people with AD, people with DLB have relatively preserved recognition memory, but greater deficits with executive function, visuospatial abilities, attention, and processing speed. This pattern can be seen on screening cognitive tests, such as the Montreal Cognitive Assessment, on which an individual with DLB would have greater problems than an individual with AD on the executive/visuospatial, attention, and verbal fluency questions, but higher memory index and orientation scores. Formal neuropsychological testing objectively measures the pattern and severity of cognitive deficits in DLB. For a DLB diagnosis, an individual must have evidence of dementia, which requires limitations in functional abilities caused by cognitive deficits (Table 1). Information on limitations in instrumental activities of daily living can be elicited from a knowledgeable informant during the history, or can be measured formally with scales such as the Functional Activities Questionnaire or the Clinical Dementia Rating scale. Research criteria also exist for MCI with Lewy bodies. A standard definition of MCI is used in the criteria (ie, cognitive complaints, objective declines in cognition, no substantial functional limitations). Individuals with MCI with Lewy bodies show early features of a DLB pattern of cognitive deficits, and are often classified as having an amnestic, multidomain pattern of MCI or a nonamnestic pattern of MCI.

### Core Clinical Features

Associated clinical symptoms and signs allow an accurate clinical diagnosis of DLB. Cognitive fluctuations, recurrent visual hallucinations, rapid eye movement (REM) sleep behavior disorder (RBD), and 1 or more cardinal features of parkinsonism on examination are used in the criteria for a clinical diagnosis of DLB (Table 1). Cognitive fluctuations can occur from day to day or may occur within a day, with
evening confusion associated with greater cognitive and psychiatric symptoms being the typical pattern (ie, “sundowning”). Clinical scales are available to measure fluctuations more objectively.14 Visual hallucinations occur early in the disease course and typically are well-formed and detailed visual perceptions. Individuals may retain insight that the hallucinations are not real, but often lose this insight as their dementia progresses. Other misperceptions such as presence delusions or misidentification delusions occur more frequently in people with DLB.

The Neuropsychiatric Inventory–Questionnaire can be used to capture symptoms of visual hallucinations and other psychiatric symptoms from a knowledgeable informant in a clinical setting.15 People with DLB commonly have features of RBD in which they physically move and act out their dreams during REM sleep. This can be measured objectively with polysomnogram recordings of sleep or by using validated scales such as the Mayo Sleep Questionnaire.16

Signs of parkinsonism are seen in almost all people with DLB. The most common signs are bradykinesia and rigidity, and, less commonly, resting tremors. Postural and kinetic tremors of the hands are common, but loss of postural stability is found only in later stages of the disease. The original UPDRS or the Movement Disorder Society–modified UPDRS (MDS-UPDRS) can be used to measure signs of parkinsonism objectively.17

Supportive Clinical Features

Many other common clinical symptoms and signs are supportive of a DLB diagnosis but not a part of the diagnostic criteria.3 These include psychiatric symptoms, such as depression and anxiety; sleep disorders, including restless legs syndrome, periodic limb movements of sleep, hypsomnoria, hyposomnia, or anosmia; and autonomic dysfunction. Common symptoms of autonomic dysfunction include constipation, orthostatic hypotension, urinary incontinence, and erectile dysfunction. People with DLB are at increased risk of delirium and may have a history of either prolonged or recurrent delirium. The research criteria for MCI-LB identify a subset of people with delirium-onset DLB.13 People with DLB are at increased risk of more severe reactions to antipsychotic medications, including development of neuroleptic malignant syndrome.

Ancillary Diagnostic Tests for DLB

Indicative Biomarkers

The revised diagnostic criteria for a clinical diagnosis of DLB describe 3 indicative biomarkers and several supportive biomarkers.3 The first indicative biomarker is reduced dopamine transporter uptake in the basal ganglia demonstrated by single-photon emission CT (SPECT) or positron emission tomography (PET), most commonly a DaTscan with the radioligand 123I-iофлупане and SPECT. Sensitivity of 78% and specificity of 90% are reported with DaTscan in differentiating DLB from AD. In the United States, the Centers for Medicare & Medicaid Services (CMS) has approved DaTscan in the diagnostic evaluation of people with possible DLB. The second indicative biomarker is polyomnographic confirmation of REM sleep without atonia (RBD). RBD often precedes other symptoms of an α-synucleinopathy (including DLB, Parkinson disease, and multiple system atrophy), and the combination of dementia and RBD strongly supports a diagnosis of DLB. The third indicative biomarker is low uptake on 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy. The MIBG scan has a sensitivity between 69% and 77% and specificity between 87% and 94% for differentiating DLB from AD, depending on the severity of the dementia stage, with better discriminative ability in milder dementia stages.

Supportive Biomarkers

Supportive biomarkers include relative preservation of medial temporal lobe structures, including the hippocampi, on structural brain imaging with head CT or brain MRI; reduced perfusion or metabolism in the occipital lobe on nuclear medicine scans (perfusion SPECT or metabolic [18F]fluorodeoxyglucose [FDG]–PET) with relative sparing of the posterior cingulate (cingulate island sign) on FDG-PET; and prominent slow-wave activity on EEG or quantitative EEG with periodic fluctuations in the pre-alpha/theta frequency range. Molecular imaging of brain α-synuclein (α-syn) pathology using SPECT or PET remains a work in progress.

Lewy Body–Specific Biomarkers

New potential diagnostic tests for Lewy body pathology show promise. Studies have been able to identify Lewy bodies in skin or other tissue biopsies.18 Another promising development is the measurement of abnormal α-syn in cerebrospinal fluid using seed amplification assays (SAAs) of misfolded α-syn with either real-time quaking-induced conversion or protein misfolding cyclic amplification techniques (α-syn–SAA).19,20 A recent meta-analysis found the pooled sensitivity of spinal fluid α-syn–SAA to be 88% and specificity 95% in differentiating people with a synucleinopathy from controls.20 These new diagnostic tests provide pathology-specific biomarkers for DLB. A new classification system uses pathology-specific biomarkers (eg, α-syn–SAA) and clinical features to identify preclinical, prodromal, and syndromic stages of synucleinopathies, including DLB.21
memory, attention, and global cognitive measures. Before adding a procholinergic medication in this class, the practitioner must lower the dose or discontinue any concomitant anticholinergic medications. Rivastigmine and donepezil have been studied extensively in people with DLB, with a high level of evidence in support of treatment, but galantamine has not been well studied. The treatment goal is to gradually increase the dose of the cholinesterase inhibitor to the maximally tolerated dose. The choice of drug and form to use depend on ease of administration, side effect profile, and cost.

As a class, cholinesterase inhibitors may cause mild to moderate side effects (in 15% to 20% of people) that may include nausea, anorexia, diarrhea, rhinorrhea, vivid dreams, and, rarely, muscle cramps, bradycardia, or syncope. People with DLB should continue a cholinesterase inhibitor even in the absence of improvement because people with DLB show less global cognitive decline over time while taking these medications. Memantine, an NMDA receptor modulator, is a second-line medication for DLB. In people with DLB on memantine, 2 randomized trials demonstrated improvement on a clinician global impression of change outcome measure, and 1 study found improvements in measures of attention and episodic recognition memory. Memantine has a good side effect profile but can cause dizziness or confusion (eg, reports of feeling detached or “spacey”) in some people. Memantine can be added to a cholinesterase inhibitor, especially in people with mild to moderate dementia symptoms and in those who may have comorbid AD pathology.

Neuropsychiatric Symptoms
People with DLB treated with cholinesterase inhibitors demonstrate improvement in neuropsychiatric symptoms on global scales, such as the Neuropsychiatric Inventory, but improvements may wane after 6 to 12 months. A meta-analysis showed that the Neuropsychiatric Inventory domains of delusions, hallucinations, and cognitive fluctuations improved in trials using donepezil. Because of the favorable side effect profile and their benefit in improving cognition, cholinesterase inhibitors can be considered first-line therapy for neuropsychiatric symptoms in people with DLB. Two placebo-controlled trials of memantine for neuropsychiatric symptoms showed mixed results.

Visual hallucinations and delusions can be disturbing to individuals with DLB and their caregivers. Research has not identified effective and safe medications to treat these symptoms. First-generation neuroleptic antipsychotics (eg, thioridazine, haloperidol) can trigger severe neuroleptic sensitivity in people with DLB, including neuroleptic malignant syndrome and fatal outcomes, and should not be used. Use of second-generation, atypical antipsychotics (eg, quetiapine, olanzapine, aripiprazole) in people with DLB has been reported in case reports, small case series, and open-label studies, with mixed results in improving psychosis, but with consistent side effects, including somnolence, worsening parkinsonism, confusion, postural instability, QTc prolongation, and rare cases of neuroleptic malignant syndrome. Clinical trials of clozapine, an atypical antipsychotic medication, and pimavanserin, a novel antipsychotic medication, in people with Parkinson disease and psychosis show efficacy in improving symptoms of psychosis without worsening parkinsonism, but have not been systematically studied in people with DLB.

Symptoms of anxiety and depression are common in people with DLB, but pharmacologic treatment of these symptoms has not been adequately studied. However, clinicians can use the approach taken by geriatric psychiatry for pharmacologic treatment of these symptoms in older adults, including trying 1 medication at a time, at very low doses, and using medications with a favorable side effect profile, including low anticholinergic burden and few drug–drug interactions.

Motor Symptoms
No double-blind, randomized controlled trials of levodopa to treat parkinsonism in people with DLB have been performed. However, open-label studies suggest that levodopa monotherapy can improve motor function in people with DLB. The degree of motor improvement is lower in people with DLB (32% to 50%) than people with PD dementia (65% to 70%). However, approximately 30% of people with DLB receiving levodopa will experience psychotic symptoms (delusions and hallucinations) after starting therapy, especially at higher doses. The anticonvulsant zonisamide has shown efficacy in a phase 2 trial when used as an adjunct to levodopa, and showed efficacy as monotherapy to treat parkinsonism in people with DLB at doses of 25 mg and 50 mg per day in a phase 3 trial, without worsening cognition or neuropsychiatric symptoms. Zonisamide was well tolerated at these doses, and UPDRS part III motor scores improved approximately 3 points when compared with the placebo group at the end of 12 weeks. Thus, low-dose levodopa should be considered in people with DLB and problematic motor symptoms, followed by either the addition or substitution of zonisamide depending on the individual’s response to levodopa.

Autonomic and Sleep Symptoms
Autonomic symptoms such as constipation, urinary incontinence, and orthostatic hypotension can be treated with standard nonpharmacologic and pharmacologic approaches in people with DLB. RBD can be severe in some people with DLB, and can be treated initially with melatonin,
and then with low-dose clonazepam if severe RBD symptoms continue. Most antidepressants can worsen RBD in up to 6% of people, but trazodone has not been associated with worsening of RBD, and can help with sleep initiation and maintenance. For people with restless legs syndrome or periodic limb movements of sleep, serum ferritin level should be checked to rule out iron deficiency, and treatment with oral iron replacement initiated if a deficiency is if found. Pharmacologic treatment options include dopamine replacement therapy and gabapentin, typically starting with gabapentin to avoid worsening neuropsychiatric symptoms with dopamine replacement therapy.

New Treatments in Development

There has been a significant increase in research funding and clinical trials of new therapeutics for people with DLB, including growth in trials of potentially disease-modifying drugs. In the United States, the Lewy Body Dementia Association (LBDA) initiated the LBDA Research Centers of Excellence program to build a well-characterized, nationwide network of individuals with DLB for rapid recruitment into therapeutic trials, and to establish infrastructure for DLB expertise, clinical trial experience, and high-quality data collection at LBDA Research Centers of Excellence sites. More information about trials recruiting participants with DLB are available at the LBDA website (https://www.lbda.org) or https://www.clinicaltrials.gov.

Conclusions

People with DLB can be diagnosed accurately with a thorough history, neurologic examination with cognitive testing, and results from ancillary tests, even in prodromal stages. Disease-specific biomarkers for Lewy body pathology are becoming available, but remain to be validated for diagnosis and staging of DLB. Effective medications are available for treatment of DLB symptoms, including cognitive, neuropsychiatric, motor, autonomic, and sleep disorder symptoms. A growing number of clinical trials including potential disease-modifying treatments for DLB offer hope for more effective treatment, and perhaps prevention, in the future.