

# Dementia With Lewy Bodies: Diagnosis and Management for Primary Care Providers

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**Objective:** The purpose of this review is to aid primary care providers in distinguishing dementia with Lewy bodies (DLB) from Alzheimer's disease and from Parkinson's disease with dementia. Differentiating these entities has important treatment implications.

**Data Sources:** A PubMed search was undertaken using the keywords *Lewy body dementia*, *dementia with Lewy bodies*, and *Lewy body disease*. There were no date restrictions. Only articles in the English language were reviewed. References of selected articles were reviewed for additional sources.

**Data Selection and Extraction:** Initially, 2,967 articles were retrieved. All 3 authors participated in data selection and extraction. Articles were further selected for content specific to epidemiology, clinical presentation, diagnostic studies, treatment, and prognosis. For articles with repetitive information, the most current article was used. This resulted in a total of 62 articles included in the review.

**Data Synthesis:** Dementia with Lewy bodies is the second leading cause of dementia after Alzheimer's disease. The core symptoms of DLB, including cognitive fluctuations, visual hallucinations, and parkinsonism, may not always be present as a triad, and clinicians may be unaware of associated symptoms. Thus, this diagnosis is frequently missed by primary care providers. Often, DLB is misdiagnosed as Alzheimer's disease, Parkinson's disease, or a primary psychiatric illness. Treatments for DLB include cholinesterase inhibitors and N-methyl-D-aspartate antagonists. Antipsychotics should be avoided or used with caution.

**Conclusions:** Dementia with Lewy bodies is an often missed diagnosis. Symptoms are often attributed to other disorders. A high clinical suspicion is helpful in accurate diagnosis, and presence of any of the core symptoms should initiate clinical suspicion of DLB. Distinguishing DLB from other disorders has important treatment implications.

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Dementia with Lewy bodies (DLB) accounts for 15% to 35% of dementia cases.<sup>1,2</sup> This disorder presents several difficulties regarding both diagnosis and management. Many patients initially present to their primary care physician. Thus, the tasks of diagnosing DLB, differentiating it from other types of dementia, and initiating evidence-based treatment often fall on primary care providers. The purpose of this review is to summarize the diagnostic criteria and clinical features, radiographic features, pathology, and treatment of this disorder to aid primary care physicians in caring for this population.

## METHOD

A PubMed search was undertaken using the keywords *Lewy body dementia*, *dementia with Lewy bodies*, and *Lewy body disease*. References of selected articles were reviewed for additional sources. Initially, 2,967 articles were retrieved. There were no date restrictions. Only articles in English were reviewed. All 3 authors participated in data selection and extraction. Articles were further selected for relevance regarding epidemiology, clinical presentation, diagnostic studies, treatment, and prognosis. For articles with repetitive information, the most current article was used. This resulted in a total of 62 articles included in the review.

## DIAGNOSTIC FEATURES

DLB is the second most common cause of dementia after Alzheimer's disease.<sup>1,2</sup> Thus, accurate recognition is crucial. Diagnostic criteria (Table 1) were initially established in 1996 and subsequently revised to improve sensitivity.<sup>3,4</sup> However, despite the revised diagnostic criteria, the recognition of DLB remains poor, with a reported rate of less than 50% in one study.<sup>5</sup> One reason for the low recognition of DLB is the difficulty associated with recognizing the diagnostic criteria. A high index of clinical suspicion is needed along with collateral information from family and caretakers.

## CLINICAL POINTS

- ◆ Dementia with Lewy bodies is an underrecognized diagnosis.
- ◆ Clinical suspicion is key to accurate diagnosis, and core symptoms should be assessed in all patients presenting with cognitive complaints.
- ◆ Cholinesterase inhibitors are the first-line treatment for dementia with Lewy bodies.

## Dementia

The diagnosis of dementia requires a gradual decline of cognitive function that impedes daily functioning and is accompanied by aphasia, apraxia, agnosia, or impaired executive function.<sup>6</sup> The pattern of cognitive deficits in DLB differs from that observed in Alzheimer's disease. Memory impairments may not be present until the latter stages of DLB. Standard bedside tests such as the Mini-Mental State Examination (MMSE) cannot reliably discriminate between DLB and other forms of dementia.<sup>3</sup> Neuropsychological testing reveals several specific deficits. When matched for age, education, and MMSE score, patients with DLB tend to demonstrate more deficits in visuo-perceptive tasks, visuoconstructive tasks, nonverbal reasoning, attention, and executive function compared to patients with Alzheimer's disease.<sup>7-13</sup> Additionally, DLB patients may show greater impairments in functional abilities earlier in the disease than Alzheimer's disease patients.<sup>14</sup> Deficits in neuropsychological testing demonstrated in DLB patients are similar to those seen in patients with Parkinson's disease with dementia.<sup>3,15</sup> Thus, neuropsychological testing is not a reliable tool to differentiate Parkinson's disease with dementia from DLB. The differentiation of these two disorders is discussed in detail later in this review.

## Fluctuating Cognition

The prevalence of fluctuating cognition in DLB has varied considerably across different studies, ranging from 30% to 89%.<sup>16,17</sup> Fluctuations vary in intensity, and their duration can range from hours to days. The variable temporal profile makes these features difficult to detect by physicians who do not see the patient for prolonged periods of time. Distinguishing the "good days" and "bad days" often reported by caregivers of Alzheimer's disease patients from the fluctuations indicative of DLB can be challenging to an inexperienced physician. It may be helpful to use validated scales such as the Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale.<sup>18,19</sup> The polarity of fluctuations can be dramatic. For example, on good days, patients may appear to be close to their previous baseline, attending to activities of daily living and participating in meaningful conversation. Hours later, they may be unable to find their bedroom, hallucinating,

and having obvious motor deficits. History from family members and caregivers is essential in determining the presence of fluctuating mental status. Clinicians are encouraged to ask about lethargy, daytime somnolence, sustained periods of staring into space, periods of decreased attention, periods of improved memory, and episodes of disorganized speech, in addition to more dramatic fluctuations as described above.<sup>4</sup> Caregivers of individuals with DLB often report observing episodes of blank staring with complete disengagement from the environment, whereas Alzheimer's disease caregivers more frequently report episodes of heightened memory impairment and repetitiveness in conversation.<sup>18,19</sup> Fluctuations in cognition in DLB tend not to be related to demands of memory function as they are with Alzheimer's disease patients. Additionally, periods of confabulation and delusional thinking are more often reported in DLB patients.<sup>18,19</sup>

## Recurrent Visual Hallucinations

The presence of recurrent complex visual hallucinations is a critical feature in differentiating between Alzheimer's disease and DLB. Hallucinations in other sensory modalities also occur, but with decreased frequency. Visual hallucinations are present earlier in the course of disease in DLB while memory may be relatively preserved. Although the presence of visual hallucinations is highly specific, the sensitivity has ranged from 39% to 77%.<sup>14,16,17</sup> Typical images include people and animals. Although the patient is aware that the images are not real, emotional responses are common.<sup>4</sup>

One caveat is that antiparkinsonian drugs commonly administered to this population because of the presence of extrapyramidal symptoms (EPS) may exacerbate or cause hallucinations. Thus, the presence of visual hallucinations with concurrent medication administration may not be as significant as hallucinations in drug-naïve patients, but this has not been systematically studied. Hallucinations that persist after antiparkinsonian medications have been withdrawn in a patient with EPS should prompt the clinician to consider DLB as the primary diagnosis.

## Spontaneous Parkinsonism

The prevalence of parkinsonism in DLB has ranged from 60% to 92%.<sup>16,17</sup> The severity of EPS is similar to

that observed in age-matched patients with Parkinson's disease.<sup>16,17</sup> Given the high rate of dementia in Parkinson's disease patients, differentiating DLB from Parkinson's disease with dementia can be difficult. It is suggested that if the onset of dementia occurs more than 12 months after the onset of motor symptoms, then *Parkinson's disease with dementia* is the appropriate label. If cognitive deficits appear within 12 months of motor symptoms, then DLB is more likely.<sup>3</sup> However, this 12-month rule is a generalization. The main point is that cognitive and motor symptoms in DLB appear close together in time, while in Parkinson's disease with dementia, cognitive deficits appear years to decades after the onset of motor symptoms. Other key differences between DLB and Parkinson's disease include a lower prevalence of resting tremor and a higher prevalence of postural instability, stooped posture, hypophonic speech, ataxia, and facial immobility in DLB compared to Parkinson's disease.<sup>3,4</sup> Additionally, responsiveness to L-dopa has been reported to be less in DLB patients compared to Parkinson's disease patients.<sup>3,4</sup> Although parkinsonism occurs in Alzheimer's disease, it tends to appear later in the course of illness than in DLB or Parkinson's disease with dementia.

### REM Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is a parasomnia characterized by the presence of vivid dreams and complex motor movement during REM sleep without muscle atonia. It predominately occurs in males and has an onset after the age of 50. Patients will act out their dreams through speech and movement, often shouting or talking with accompanying limb flailing and/or falling out of bed. Violent behavior can also occur. Iranzo et al<sup>20</sup> reported on a series of 17 patients with RBD and DLB. Self-awareness of behaviors was present in 29% of patients, and the recollection of unpleasant dreams, in 82%. Unpleasant dreams most frequently involved being attacked by someone, arguing with someone, and being chased by someone. The most frequently reported behaviors in descending order were talking, shouting, falling out of bed, punching, and laughing. Forty percent of patients reported sustaining injuries, and 6% injured their bed partner.<sup>20</sup> Often the history is obtained from a bed partner, and symptoms can be present for decades before the onset of dementia.<sup>21,22</sup>

Idiopathic RBD can be a harbinger of a subsequent neurodegenerative disease, namely the  $\alpha$ -synucleinopathies (Parkinson's disease, multiple system atrophy, and DLB). The prevalence of polysomnogram-confirmed RBD in patients with  $\alpha$ -synucleinopathies is 39% versus 0% in patients with nonsynucleinopathies (Alzheimer's disease, frontotemporal dementia, corticobasal degeneration, progressive supranuclear palsy, mild cognitive impairment, primary progressive

aphasia, and posterior cortical atrophy).<sup>23</sup> The frequency of probable RBD in Parkinson's disease and DLB patients compared to those with Alzheimer's disease and mild cognitive impairment was 56% versus 2%.<sup>23</sup> In 10 autopsied patients with clinically diagnosed RBD, 9 had Lewy body disease.<sup>23</sup> The estimated 10-year risk of developing a neurodegenerative disease has been reported to be 40% in patients with RBD.<sup>24</sup> The reported risk of development of DLB has ranged from 7% to 14% in patients presenting with idiopathic RBD.<sup>22,24</sup> The exact prevalence of RBD in patients with DLB is unknown. However, studies have suggested rates of 50% to 83%.<sup>17</sup>

Clinicians with patients diagnosed with idiopathic RBD should monitor for DLB as the patient ages, and in patients suspected of having dementia, the presence of RBD should prompt consideration of DLB as the primary diagnosis.

### Neuroleptic Sensitivity

Primary care providers understandably may consider the use of antipsychotics in this population. However, the decision to utilize these medications is not without significant risk. In a series of 20 patients with DLB, McKeith et al<sup>25</sup> reported that 80% received neuroleptics. Of those, 46% developed EPS for the first time after neuroleptic administration. Additionally, 81% of patients receiving antipsychotics developed a neuroleptic sensitivity syndrome ranging from mild (54%) to severe (46%). A mild syndrome was characterized by increased tone, rigidity, or bradykinesia. Severe reactions were characterized by sudden onset of sedation, immobility, fever, and confusion at times resembling neuroleptic malignant syndrome. Patients suffering severe reactions did not differ in age, sex, presence of psychosis, EPS at presentation, or syncopal episodes from those not suffering severe reactions. Severe reactions were also associated with a 2-fold increase in mortality. In a follow-up study, Ballard et al<sup>26</sup> found that 29% of DLB patients receiving neuroleptics had severe reactions, half of whom died within 2 months.

### Supportive Features

As highlighted in Table 1, there are several features that support a diagnosis of DLB, but are not specific enough to allow definitive diagnosis. Autonomic instability is also present in other  $\alpha$ -synucleinopathies and, in addition to parkinsonism, may predispose patients to falls or syncope. In turn, patients may come to clinical attention because of repeated falls or syncopal episodes. McKeith et al<sup>25</sup> found that 35% of DLB patients reported repeated unexplained falls, while 25% endorsed syncopal episodes at presentation. In patients presenting with frequent falls or loss of consciousness, cognitive deficits may be elicited only through careful questioning. Psychiatric symptoms including depression,

**Table 1. Criteria for Diagnosis of Dementia With Lewy Bodies (DLB)<sup>a</sup>**

Central features (most be present for possible or probable DLB)
Dementia defined as progressive cognitive decline of sufficient amount to interfere with normal social or occupational function
Prominent or persistent memory impairment may not necessarily occur in early stages but becomes evident with disease progression
Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent
Core features (2 core features are needed for probable DLB, 1 for possible DLB)
Fluctuating cognition
Recurrent visual hallucinations
Spontaneous features of parkinsonism
Suggestive features (If 1 or more of these is present in addition to 1 or more core features, a diagnosis of probable DLB can be made. If no core features are present but more than 1 suggestive feature is present, then possible DLB can be diagnosed. Probable DLB cannot be diagnosed without the presence of core features)
REM sleep behavior disorder
Severe neuroleptic sensitivity
Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging
Supportive features (commonly present but not proven to have diagnostic specificity)
Frequent falls/syncope
Unexplained loss of consciousness
Autonomic dysfunction
Nonvisual hallucinations
Systematic delusions
Depression
Preservation of medial temporal lobes on imaging
Low uptake MIBG myocardial scintigraphy
Slow-wave activity on EEG with transient sharp waves in temporal lobe
A diagnosis of DLB is less likely if
Presence of cerebral vascular disease is evident by focal neurologic signs/imaging
Presence of other illness is sufficient to account for symptoms
Parkinsonism appears for the first time at a stage of severe dementia

<sup>a</sup>Based on McKeith et al.<sup>3</sup>

Abbreviations: EEG = electroencephalogram, MIBG = meta-iodobenzylguanidine, PET = positron emission tomography, REM = rapid eye movement, SPECT = single-photon emission computed tomography.

anxiety, and psychosis are common. In a series of 92 DLB patients, Borroni et al<sup>27</sup> found that 67% reported anxiety, 62% endorsed depression, 58% complained of apathy, and half the sample had psychotic symptoms. Psychotic symptoms including delusions and hallucinations, and anxiety worsened with disease progression, although depression remained stable. No relationship between neuropsychiatric symptoms and motor symptoms was observed. McKeith et al<sup>25</sup> found that 45% of DLB patients endorsed auditory hallucinations, while 80% had delusions at some point during their illness.

### Radiographic Features

Clinically, differentiating DLB and other dementia subtypes such as Parkinson's disease with dementia and Alzheimer's disease can be difficult. Considering poor sensitivity of the diagnostic criteria, it is important to look at additional distinguishing investigations to improve diagnostic precision.<sup>5</sup> The American Academy of Neurology<sup>28</sup> recommends structural neuroimaging with either noncontrast head computed tomography (CT) or magnetic resonance imaging (MRI) in the routine initial evaluation of all patients with dementia to rule out malignancy, normal pressure hydrocephalus, and subdural hematomas as possible causes.

An MRI is more sensitive than a CT scan for studying regional changes in tissue volume in the brain. Alzheimer's disease is characteristically defined by diffuse

cerebral atrophy with a disproportionate amount in the medial temporal lobes with relative sparing of subcortical structures. Ventricular enlargement also is present as disease progresses.<sup>29</sup> Conversely, DLB and Parkinson's disease with dementia show similar changes on MRI consisting of atrophy of subcortical structures including the basal ganglia with relative preservation of medial temporal lobe structures.<sup>3</sup> Additionally, DLB patients show slower rates of cerebral atrophy and ventricular enlargement compared to Alzheimer's disease patients.<sup>29</sup>

Of increasing interest in differentiating Alzheimer's disease from DLB are functional neuroimaging studies that examine cerebral perfusion and cerebral metabolism utilizing single-photon emission computed tomography (SPECT) or positron emission tomography (PET), respectively. This stems from the hypothesis that even those with DLB without parkinsonism will show degeneration in the nigrostriatal system, whereas those with Alzheimer's disease will not. Using molecules that bind to the dopamine reuptake and transporter molecule found in presynaptic membranes of dopamine-producing neurons in the caudate and putamen, SPECT can be used to measure the density of dopaminergic neurons in the nigrostriatal system. Thus, reduced dopamine transporter binding has been proposed as a means to differentiate between DLB and Alzheimer's disease.<sup>30</sup> In a series of 23 patients with dementia, Walker and Walker<sup>30</sup> found that the sensitivity and specificity for diagnosing



DLB via SPECT was 100% and 92%, respectively. Other studies<sup>31–33</sup> have reported abnormal dopamine transporter scans to have a sensitivity of over 75% and a specificity of over 90% for DLB. PET scans have shown hypometabolism in the posterior cortical region as well, which is thought to explain the increased incidence of visual hallucinations in this population versus Alzheimer's disease. Both SPECT and PET scanning appeared useful for the diagnosis of DLB, but SPECT provided more robust results than PET.<sup>34</sup> However, lack of availability limits the use of all functional neuroimaging.

Although an electroencephalogram (EEG) is not routinely done in evaluation of dementia, several investigators have examined its diagnostic utility. Bonnani et al<sup>35</sup> identified slow activities (pre- $\alpha$ ) in posterior derivations of all DLB patients that notably differentiated these patients from those with Alzheimer's disease. Intermittent delta and sharp transients also occur more in patients with DLB than those with Alzheimer's disease, although their frequency may be too small to aid in diagnosis.<sup>3,35</sup> In short, EEG is not a useful tool in identifying DLB.

The role of biomarkers, including tau and amyloid  $\beta$  42 concentrations in cerebrospinal fluid, in diagnosing dementia has garnered increased clinical attention recently and may have some diagnostic relevance. However, routine use of biomarkers in diagnosis is not recommended at this time by the American Academy of Neurology.<sup>28,36</sup>

## **PATHOLOGY**

Pathological assessment of DLB reveals aggregates of  $\alpha$ -synuclein, referred to as *Lewy bodies*, found in neurons and glia. They are hypothesized to stem from abnormal protein processing giving rise to cytoplasmic inclusions identifiable by immunohistochemistry.<sup>37</sup> Their presence is required for the DLB diagnosis at autopsy. Brainstem involvement is almost universal, and variable amounts of Lewy body burden are found in the limbic system and neocortex.<sup>3,38</sup> In addition to central nervous system involvement, Lewy bodies are also found in the peripheral nervous system and autonomic nervous system and thought to be related to orthostasis.<sup>38</sup> There is some sense that the location of Lewy bodies relates to neural dysfunction. Brainstem lesions are thought to account for EPS, while cognitive and neuropsychiatric symptoms are attributed to neocortical and limbic involvement. However, despite the intuitive nature of this hypothesis, the burden of Lewy bodies in specific brain regions has not been conclusively demonstrated to correlate with clinical symptoms. Whether Lewy bodies are involved in neurodegeneration directly, a cellular defense mechanism, or by-products of an unidentified degenerative process has yet to be determined.<sup>38</sup>

Additionally, the mere presence of Lewy bodies is not in itself enough to cause clinical symptoms. In fact, an estimated 24% to 55% of neuropsychiatrically healthy elderly adults are found to have significant Lewy bodies.<sup>38</sup> Confounding the pathological picture is the high incidence of comorbid Alzheimer's pathology, which is present in 35% to 90% of cases.<sup>39</sup>

Similar to Alzheimer's disease, DLB is also associated with deficiencies in cholinergic transmission. Additionally, relative to patients with Alzheimer's disease, those with DLB have lower choline acetyltransferase activity.<sup>40–43</sup> It has been hypothesized that the increased prevalence of psychotic symptoms and visuospatial dysfunction in DLB patients may be secondary to the greater deficits in cholinergic transmission.<sup>40–43</sup> Reduced activity of choline acetyltransferase in the temporal and parietal neocortex has been observed in DLB patients and correlated with the presence of visual hallucinations, while up-regulation of muscarinic  $M_1$  postsynaptic receptors in the temporal lobe has been correlated with delusional thinking.<sup>43,44</sup> Relative to Alzheimer's disease, DLB is also associated with reductions in dopamine in the basal ganglia and norepinephrine in the putamen.<sup>41</sup> Abnormalities in glutamate receptors and second messenger signaling have also been demonstrated.<sup>45</sup>

## **TREATMENT**

### **Cognitive Symptoms**

The marked decrease in cholinergic functioning observed in DLB patients relative to Alzheimer's disease patients led to speculation that cholinesterase inhibitors (ChEIs) may have a greater potential for improvement in DLB than in Alzheimer's disease. Additionally, the observation of less neuronal loss in DLB than in Alzheimer's disease suggests that cortical neurons in DLB are more viable than those in Alzheimer's disease and could be more responsive to cholinergic stimulation.<sup>29,41</sup> Studies have not confirmed this hypothesis, though.

Patients with DLB who are treated with ChEIs have shown improvement in various neuropsychiatric measures. In a placebo-controlled, double-blind study conducted in 120 patients with DLB, McKeith et al<sup>46</sup> found significant improvements in measures of attention as well as reductions in psychotic symptoms. There was no observed mortality benefit. In a prospective, randomized, double-blind, placebo-controlled trial involving 92 DLB patients treated with rivastigmine, Wesnes et al<sup>47</sup> observed improvements in measures of attention, working memory, and episodic memory. Grace et al<sup>48</sup> observed improvements in MMSE scores and neuropsychiatric symptoms over 24 weeks, a finding that has been observed by others.<sup>49</sup> Grace and colleagues' study was extended over 96 weeks, and neither MMSE nor Neuropsychiatric Inventory scores significantly

differed from baseline, suggesting that ChEIs may attenuate degeneration.<sup>48</sup> This hypothesis is further supported by findings by Ballard et al,<sup>50</sup> who observed a 70% reduction in amyloid  $\beta$  pathology in autopsies of 12 patients with DLB receiving ChEI therapy versus patients not receiving such therapy. Groups were matched for age as well as duration and severity of dementia.

Galantamine has also been studied. It not only is a ChEI but also allosterically modulates neuronal nicotinic receptors. In patients with DLB, there is a selective loss of the  $\alpha_7$  nicotinic receptors in the hippocampus, suggesting possible added benefits of galantamine for cognition and behavior due to its selective nicotinic receptor modulation. One study<sup>51</sup> showed substantial benefits in visual hallucinations and fluctuating cognitive deficits. Finally, donepezil has also shown positive results in measures of cognition and neuropsychiatric symptoms.<sup>52,53</sup> Differences between ChEIs have not been found,<sup>54</sup> although head-to-head trials are lacking.

Thus, it appears that all ChEIs can be effective in this population. However, results should be viewed cautiously, as the number of trials is small, with few being placebo controlled, and the number of patients is limited. Additionally, although results suggest statistically significant improvement in symptoms, it is uncertain whether these correspond to clinically significant differences. To date, there has been no mortality benefit with any pharmacologic treatment of DLB, and the clinical course tends to be one of progressive deterioration.

Given the observed aberrations observed in glutaminergic transmission, it seems intuitive that the *N*-methyl-D-aspartate antagonist memantine may have a role in treatment. Memantine has been shown to decrease neuropsychiatric symptoms including aggression and disinhibition, as well as Clinical Global Impression of Change and MMSE scores.<sup>55–57</sup>

### Neuropsychiatric Symptoms

DLB patients suffer from a variety of neuropsychiatric symptoms, as discussed previously, including anxiety, depression, and psychosis. Comorbid anxiety and depression is best addressed with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).<sup>3</sup> There are no studies showing differences between SSRIs or SNRIs. However, it makes intuitive sense that those with stronger anticholinergic side effects such as paroxetine may not be the best first-line agents. Tricyclic antidepressants and other antidepressants with anticholinergic properties are best avoided, as they can worsen cognition and visual hallucinations. Efforts should also be made to avoid benzodiazepines, as they can worsen cognition and predispose this vulnerable population to falls. However, at times they may be necessary, particularly for RBD. In these cases, very low doses of clonazepam can be

administered prior to bedtime. Other agents showing effectiveness in RBD include melatonin and very small doses of quetiapine.<sup>3,58,59</sup> The latter should be used with caution, however, because of enhanced neuroleptic sensitivity.<sup>3</sup> Apathy and aggression may respond to ChEIs and memantine, as mentioned above. Psychotic symptoms may improve with ChEIs.<sup>46,51</sup> However, if the symptoms are refractory to this treatment and cause significant impairment and burden to caregivers, second-generation antipsychotics such as quetiapine and clozapine can be used in lower doses with caution and attention to neuroleptic sensitivity. This course of action involves a careful discussion with family members about the risk of neuroleptic sensitivity as well as the US Food and Drug Administration black box warning regarding use of these medications in patients with dementia. Unfortunately, there are no clear-cut guidelines to aid clinicians. If the question of antipsychotic use arises, referral to a specialist is appropriate.

### Motor Symptoms

Motor symptoms can be particularly disabling for patients. Dopaminergic agents are typically administered for parkinsonism, but their use must be balanced against the risk of exacerbation of psychotic symptoms. Additionally, patients with DLB show a lower response than those with Parkinson's disease, and it has been suggested that this be a distinguishing diagnostic feature.<sup>3</sup> In a series of 14 patients with DLB, Molloy et al<sup>60</sup> found that after an acute single-dose challenge with L-dopa, only 36% demonstrated a response, defined as a 20% or greater improvement in 2 of 3 tests of motor function on the Unified Parkinson's Disease Rating Scale (UPDRS). Seventy percent of Parkinson's disease with dementia patients and 57% of Parkinson's disease patients were classified as responders. Medication dosage did not differ significantly between groups.<sup>60</sup> Bonelli et al<sup>61</sup> found a greater than 20% improvement in UPDRS scores in 50% of DLB patients compared to 65% of Parkinson's disease with dementia patients and 90% of Parkinson's disease patients. Adverse events were not reported. Goldman et al<sup>62</sup> reported improvement in motor symptoms in 6 of 19 DLB patients. Of the responders, 2 developed worsening hallucinations. Thus, only 22% of the cohort was able to achieve improvement in motor symptoms without exacerbation of psychosis.

Further research is required to determine the pathophysiology underlying these results, but they suggest a fundamental difference in disease process. Hypotheses put forward to explain these differences include intrinsic  $\alpha$ -synuclein pathology in the striatal system, loss of dopamine receptors in the caudate and putamen, and loss of dopamine receptors on corticostriatal projections.<sup>60</sup> Other antiparkinsonian medications besides L-dopa, including selegiline, amantadine, catechol-O-methyl

Table 2. Clinical Studies in Treatment of Dementia With Lewy Bodies

Author	No. of Subjects	Duration	Assessment Scales	Intervention	Outcome
McKeith et al, 2000 <sup>46</sup>	120 DLB patients	20 wk	NPI, MMSE, CGI-C	Trial of rivastigmine	With intent to treat, no difference in NPI, MMSE, CGI-C, or mortality. However, improvement in NPI of DLB patients was noted when analysis was restricted to observed cases
Wesnes et al, 2002 <sup>47</sup>	92 DLB patients	20 wk with 3-wk posttreatment follow-up	Cognitive Drug Research computerized assessment system, NPI	Trial of rivastigmine	Improvement in attention episodes and working memory with rivastigmine compared to placebo. Three wk after discontinuation of rivastigmine, cognitive performance returned to baseline
Grace et al, 2001 <sup>48</sup>	29 DLB patients (9 women and 20 men) in 3 centers; randomized, placebo-controlled trial of rivastigmine	96 wk	MMSE, NPI	Treatment with rivastigmine	After 24 wk, MMSE and NPI scores were improved. At 96 wk, neither MMSE nor NPI scores were worse than at baseline
Rozzini et al, 2007 <sup>49</sup>	30 DLB patients and 30 AD patients	16 wk	MMSE, NPI, BPSD	Treatment with rivastigmine	At baseline, DLB compared to AD patients showed a greater number of EPS and were similar in cognitive symptoms and BPSD. After treatment, both groups showed a comparable cognitive improvement in both groups, with significant behavioral effect in DLB but not AD patients in hallucinations and sleep disorders
Ballard et al, 2007 <sup>50</sup>	Autopsy of 12 DLB patients treated with donepezil, rivastigmine, tacrine, and galantamine and 12 untreated patients	Mean treatment duration of 24.8 mo	Cortical $\beta$ amyloid and tau pathologies on autopsy	6 patients treated with donepezil, 4 with rivastigmine, and 1 each with tacrine and galantamine	Treated patients with DLB had significantly (70%) less parenchymal amyloid $\beta$ deposition compared to untreated patients
Edwards et al, 2007 <sup>51</sup>	50 DLB patients	24-wk open-label study	NPI, CGI-C, Cognitive Assessment System	Efficacy and safety of galantamine in DLB	Treatment resulted in significant improvements in NPI and CGI-C scores. Adverse events were mild and transient
Shea et al, 1998 <sup>52</sup>	9 DLB patients	12-wk open-label study	Neuropsychiatric symptoms, MMSE	Treatment with donepezil	Eight of 9 patients demonstrated improvement in hallucinations. Cognition improved in 7 of 9 patients
Thomas et al, 2005 <sup>53</sup>	30 DLB patients and 40 PDD patients	20 wk	MMSE, NPI, UPDRS III <sup>a</sup>	Open-label treatment with donepezil	After 20 wk, each group showed significant improvements from baseline in NPI and MMSE, but no between-group differences were noted. UPDRS scores did not significantly differ from baseline
Bhasin et al, 2007 <sup>54</sup>	Comparison of 3 treatments at 12 and 20 wk: Thomas et al (2005), 29 patients treated with donepezil; Edwards et al (2004), 42 patients treated with galantamine; McKeith et al (2000), 35 patients treated with rivastigmine	12 and 20 wk	NPI, MMSE, UPDRS III <sup>a</sup>		All acetylcholinesterase inhibitors significantly improved cognitive and neuropsychiatric measures. No compelling evidence that any one ChEI is better than another in the treatment of DLB
Emre et al, 2010 <sup>55</sup>	199 Patients: 34 DLB patients and 62 PDD patients treated with memantine; 41 DLB patients and 58 PDD patients treated with placebo	24 wk	NPI, CGI-C	Efficacy and safety of memantine	Patients with DLB who received memantine showed greater improvement on NPI and CGI-C than those who received placebo
Aarsland et al, 2009 <sup>56</sup>	32 DLB patients and 40 PDD patients	24-wk randomized controlled trial	Effect of memantine on CGI-C	Treatment with memantine in patients with PDD or DLB	Memantine group had better CGI-C scores compared to placebo. No between-group differences noted
Levin et al, 2009 <sup>57</sup>	23 DLB patients in 2 groups: 14 treated with memantine and 9 control group	16-wk open-label study	CAF, MDS, MMSE, UPDRS	Efficacy and safety of memantine in DLB	Patients showed significant improvement on MMSE, MDS, CAF, aggression, lack of spontaneity, disinhibition. No change in severity of psychosis or motor disorder
Molloy et al, 2005 <sup>60</sup>	14 DLB patients, 33 PDD patients, and 31 PD patients	6 mo	UPDRS III <sup>a</sup> scores	L-dopa treatment for EPS	Acute L-dopa challenge resulted in response in 36% of DLB patients compared to 70% of PDD and 57% of PD patients
Bonelli et al, 2004 <sup>61</sup>	20 DLB patients, 20 PDD patients, and 20 PD patients	L-dopa challenge	UPDRS III <sup>a</sup> scores	L-dopa treatment for EPS	Greater than 20% improvement noted in 50% of DLB patients compared to 65% of PDD and 90% of PD patients
Goldman et al, 2008 <sup>62</sup>	19 Subjects fulfilling probable DLB consensus criteria	Approximately 4 mo	UPDRS III <sup>a</sup> scores	Treatment with L-dopa	Motor benefit without exacerbation of psychosis was seen in only 4 (22%) of DLB patients. Dopaminergic medication had limited benefit in DLB patients because of low likelihood of motor improvement and the risk of psychosis exacerbation

<sup>a</sup>Total motor score of the UPDRS.

Abbreviations: AD = Alzheimer's disease, BPSD = behavioral and psychological symptoms of dementia, CAF = Clinical Assessment of Fluctuation, CGI-C = Clinical Global Impression of Change, ChEI = cholinesterase inhibitor, DLB = dementia with Lewy bodies, EPS = extrapyramidal symptoms, MADRS = Montgomery-Asberg Depression Rating Scale, MDS = Mattis Dementia Scale, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, PD = Parkinson's disease, PDD = Parkinson's disease with dementia, UPDRS = Unified Parkinson's Disease Rating Scale.

transferase inhibitors, anticholinergics, and dopamine agonists, should be used with caution in view of concerns about inducing confusion and psychosis.<sup>62</sup>

Thus, the decision to use dopaminergic agents must be undertaken with caution. Clinicians are advised to start with low doses and titrate slowly, with constant monitoring for worsening cognition and psychosis.

Management of orthostatic hypotension consists of elimination of offending medications, increased water intake, and use of ankle pumps and compression stockings. If these measures are ineffective, fludrocortisone and midodrine may be tried.<sup>63,64</sup>

A summary of clinical studies involving treatment is presented in Table 2.

### Nonpharmacologic Treatment

Given the limited efficacy of medications for this disease and the substantial burden caregivers encounter, it is important to encourage families to use nonpharmacologic treatment strategies. These include using walkers and canes to minimize the risk of falls as well as using ramps instead of stairs and installing grab bars.<sup>63</sup> Physical therapy and occupational therapy are appropriate referrals to aid in maintaining mobility and preventing falls.<sup>63</sup> Keeping patients away from heavy machinery to prevent injury and removing driving privileges are important components of care. Finally, caregivers should be given education and monitored for caregiver burnout, as DLB patients often require around-the-clock care as the disease progresses. Providers should initiate conversations of nursing home and extended care facility placement with families. Additionally, code status and conversations regarding end-of-life issues need to take place early in the disease process while the patient can still participate.

### PROGNOSIS

The prognosis of DLB is poor. Jellinger et al<sup>65</sup> found a median time of survival of 5 years from symptom onset in a series of 243 autopsy-confirmed cases of DLB and Parkinson's disease. Williams et al<sup>66</sup> found a median survival of 7.3 years after onset of dementia. Relative to Alzheimer's disease, DLB is associated with increased overall mortality and reduced survival after onset of dementia in some but not all studies. The time to institutionalization and rate of cognitive decline is similar between the 2 illnesses. These effects are independent of baseline cognitive status, comorbidities, and medications. Male gender has been reported to be a risk factor for increased mortality in some but not all studies.<sup>65–68</sup>

### CONCLUSION

Dementia with Lewy bodies is a common cause of dementia in the elderly. It is a diagnosis that is often missed because of the difficulty in obtaining core symptoms. Often, patients are not forthcoming with psychiatric symptoms and may only endorse cognitive impairment or motor symptoms, leading to a misdiagnosis of Alzheimer's disease or Parkinson's disease. Additionally, patients presenting with psychotic symptoms may be misdiagnosed with a primary psychotic disorder. Accurate diagnosis is critical in order to avoid using neuroleptics and antiparkinsonian agents in this population. Patients presenting with motor symptoms or repeated falls should be carefully questioned about cognitive and psychiatric symptoms. Similarly, older patients presenting with new-onset psychotic symptoms should have a thorough evaluation, including neuropsychiatric testing, before their complaints are attributed to a late-onset primary psychotic disorder. Additional history should be obtained from family members or caregivers, as patients may not have insight into their symptoms. Education should be provided to family members about the overall prognosis and nature of psychotic symptoms, as these can be particularly distressing to caregivers.

**Drug names:** amantadine (Symmetrel and others), clonazepam (Klonopin and others), clozapine (Clozaril, FazaClo, and others), donepezil (Aricept and others), galantamine (Razadyne), memantine (Namenda), midodrine (Proamatine and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), rivastigmine (Exelon and others), selegiline (Eldepryl and others), tacrine (Cognex).

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