

# Differentiating Alzheimer's disease from dementia with Lewy bodies



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## How to accurately distinguish the 2 most common causes of neurodegenerative dementia

**A**lzheimer's disease (AD) and dementia with Lewy bodies (DLB) are the first and second most common causes of neurodegenerative dementia, respectively.<sup>1,2</sup> Although the pathogenetic mechanisms underlying AD and DLB are different, there are extensive clinical, pathological, and biochemical overlaps.<sup>3,4</sup> Accurate diagnosis of these disorders has therapeutic, prognostic, and research implications, including:

- compared with AD patients, DLB patients may be more sensitive to antipsychotics
- AD and DLB patients may respond differently to cholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonists
- AD and DLB have genetic implications
- Accurate diagnosis may eventually lead to disease-modifying treatments.

Diagnostic accuracy in DLB improved with use of revised criteria from the third report of the DLB Consortium in 2005,<sup>5</sup> but still is imperfect. Biomarkers for AD and DLB are needed. A thorough evaluation of cognitive and neurobehavioral symptoms coupled with imaging markers could provide a more accurate approach for differentiating AD and DLB. This article reviews the clinical manifestations, diagnostic evaluation, and management of AD and DLB.

### Epidemiology and genetics

AD is the most common form of dementia, accounting for approximately two-thirds of dementia cases and 60% to 70% of cases of progressive cognitive impairment in older adults.<sup>6</sup> In

Table 1

## Diagnostic criteria for AD and DLB

### NIA-AA criteria for AD (2011)<sup>10</sup>

**Possible AD:** Clinical and cognitive criteria (DSM-IV-TR) for AD are met and there is an absence of biomarkers to support the diagnosis or there is evidence of a secondary disorder that can cause dementia

**Probable AD:** Clinical and cognitive criteria for AD are met and there is documented progressive cognitive decline or abnormal biomarker(s) suggestive of AD or evidence of proven AD autosomal dominant genetic mutation (presenilin-1, presenilin-2, amyloid- $\beta$  precursor protein)

**Definite AD:** Clinical criteria for probable AD are met and there is histopathologic evidence of the disorder

### Revised clinical diagnostic criteria for DLB (2005)<sup>5</sup>

**Core features:** Fluctuating cognition, recurrent visual hallucinations, soft motor features of parkinsonism

**Suggestive features:** REM sleep behavior disorder, severe antipsychotic sensitivity, decreased tracer uptake in striatum on SPECT dopamine transporter imaging or on myocardial scintigraphy with MIBG

**Supportive features (common but lacking diagnostic specificity):** repeated falls and syncope; transient, unexplained loss of consciousness; systematized delusions; hallucinations other than visual; relative preservation of medial temporal lobe on CT or MRI scan; decreased tracer uptake on SPECT or PET imaging in occipital regions; prominent slow waves on EEG with temporal lobe transient sharp waves

AD: Alzheimer's disease; DLB: dementia with Lewy bodies; MIBG: metaiodobenzylguanidine; NIA-AA: National Institute on Aging and the Alzheimer's Association; PET: positron emission tomography; REM: rapid eye movement; SPECT: single photon emission computed tomography

## Clinical Point

Memory impairment in DLB usually appears later in the disease course than in Alzheimer's disease

a review of 6 studies, the prevalence of DLB ranged from 0% to 5% in the general population and from 0% to 31% among dementia patients.<sup>7</sup> Similar to AD, DLB becomes more prevalent with age; mean age at presentation is 75 years. In contrast to AD, DLB seems to be more common among men.<sup>8</sup>

A family history of AD is a significant risk factor for developing AD. Approximately 30% to 40% of early onset (age <65) AD cases are caused by mutations in the amyloid precursor protein, presenilin 1, or presenilin 2 gene. The apolipoprotein E-e4 (APOE e4) allele is a risk factor for late-onset AD. APOE e4 has little effect on disease onset or duration in DLB but its presence reduces survival time in DLB, as it does in AD.<sup>9</sup> Although most cases of DLB are sporadic, several cases of familial DLB have been reported.

For a discussion of the neuropathology of AD and DLB, see this article at CurrentPsychiatry.com.

## Evolving diagnostic criteria

Extensive research has increased our understanding of AD, which is reflected in AD

criteria proposed in 2011 by the National Institute on Aging and the Alzheimer's Association workgroup (Table 1).<sup>5,10</sup> For a review of these criteria, see "New Alzheimer's disease guidelines: Implications for clinicians," CURRENT PSYCHIATRY, March 2012, p. 15-20; <http://bit.ly/UNYikk>.

The 2005 report of the DLB Consortium<sup>5</sup> recognizes central, core, suggestive, and supportive features of DLB (Table 1).<sup>5,10</sup> These features are considered in the context of other confounding clinical conditions and the timing of cognitive and motor symptoms. The revised DLB criteria<sup>5</sup> require a central feature of progressive cognitive decline. "Probable DLB" is when a patient presents with 2 core features or 1 core feature and  $\geq 1$  suggestive features. A diagnosis of "possible DLB" requires 1 core feature or 1 suggestive feature in the presence of progressive cognitive decline.

## Biomarkers for AD, but not DLB

The 2011 diagnostic criteria for AD incorporate biomarkers that can be measured in vivo and reflect specific features of disease-related pathophysiologic processes. Biomarkers for

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## Differentiating dementias

### Clinical Point

Visual hallucinations, usually well-formed perceptions of insects, animals, or people, are the defining feature of DLB



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AD are divided into 2 categories:<sup>11</sup>

- amyloid-beta (A $\beta$ ) accumulation: abnormal tracer retention on amyloid positron emission topography (PET) imaging and low cerebrospinal fluid (CSF) A $\beta$ <sub>42</sub>
- neuronal degeneration or injury: elevated CSF tau (total and phosphorylated tau), decreased fluorodeoxyglucose uptake on PET in temporo-parietal cortices, and atrophy on structural MRI in the hippocampal and temporo-parietal regions.

No clinically applicable genotypic or CSF markers exist to support a DLB diagnosis, but there are many promising candidates, including elevated levels of CSF p-tau 181, CSF levels of alpha- and beta-synuclein,<sup>12</sup> and CSF beta-glucocerebrosidase levels.<sup>13</sup> PET mapping of brain acetylcholinesterase activity,<sup>14</sup> 123I-2 $\beta$ -carbomethoxy-3 $\beta$ -(4-iodophenyl)-N-(3-fluoropropyl)nortropane single photon emission computed tomography (SPECT) dopamine transporter (DaT) imaging<sup>15</sup> and metaiodobenzylguanidine (MIBG) scintigraphy also are promising methods. DaT scan SPECT is FDA-approved for detecting loss of functional dopaminergic neuron terminals in the striatum and can differentiate between AD and DLB with a sensitivity and specificity of 78% to 88% and 94% to 100%, respectively.<sup>16</sup> This test is covered by Medicare for differentiating AD and DLB.

### Differences in presentation

**Cognitive impairment.** Contrary to the early memory impairment that characterizes AD, memory deficits in DLB usually appear later in the disease course.<sup>5</sup> Patients with DLB manifest greater attentional, visuospatial, and executive impairments than those with AD, whereas AD causes more profound episodic (declarative) memory impairment than DLB. DLB patients show more preserved consolidation and storage of verbal information than AD patients because of less neuroanatomical and cholinergic compromise in the medial temporal lobe. There is no evidence of significant differences in remote memory, semantic memory, and language (naming and fluency).

Compromised attention in DLB may be the basis for fluctuating cognition, a characteristic of the disease. The greater

attentional impairment and reaction time variability in DLB compared with AD is evident during complex tasks for attention and may be a function of the executive and visuospatial demands of the tasks.<sup>17</sup>

Executive functions critical to adaptive, goal-directed behavior are more impaired in DLB than AD. DLB patients are more susceptible to distraction and have difficulty engaging in a task and shifting from 1 task to another. This, together with a tendency for confabulation and perseveration, are signs of executive dysfunction.

**Neuropsychiatric features.** DLB patients are more likely than AD patients to exhibit psychiatric symptoms and have more functional impairment.<sup>18</sup> In an analysis of autopsy-confirmed cases, hallucinations and delusions were more frequent with Lewy body pathology (75%) than AD (21%) at initial clinical evaluation.<sup>18</sup> By the end stages of both illnesses, the degree of psychotic symptoms is comparable.<sup>19</sup> Depression is common in DLB; whether base rates of depressed mood and major depression differ between DLB and AD is uncertain.<sup>20</sup>

Psychosis in AD can be induced by medication or delirium, or triggered by poor sensory perceptions. Psychotic symptoms occur more frequently during the moderate and advanced stages of AD, when patients present with visual hallucinations, delusions, or delusional misidentifications. As many as 10% to 20% of patients with AD experience hallucinations, typically visual. Delusions occur in 30% to 50% of AD patients, usually in the later stages of the disease. The most common delusional themes are infidelity, theft, and paranoia. Female sex is a risk factor for psychosis in AD. Delusions co-occur with aggression, anxiety, and aberrant motor behavior.

Visual hallucinations—mostly vivid, well-formed, false perceptions of insects, animals, or people—are the defining feature of DLB.<sup>21</sup> Many patients recognize that they are experiencing visual hallucinations and can ignore them. DLB patients also may experience visual illusions, such as misperceiving household objects as living beings. Delusions—typically paranoid—are common among DLB patients,

Table 2

## Diagnostic testing for Alzheimer's disease and dementia with Lewy bodies

### Alzheimer's disease

### Dementia with Lewy bodies

Neuropsychological testing findings	
Relatively more impairment on verbal memory tasks, delayed recall, delayed recognition, and encoding and storing information. <sup>28</sup> Dysfunction of episodic memory function	Relatively more impairment on attention or concentration, verbal fluency, visuoperceptual, visuoconstructive, visual memory tests, and frontal executive functions. <sup>28</sup> Relatively preserved confrontation naming and verbal memory
MRI findings	
Diffuse cortical atrophy, relatively greater volume loss in hippocampus and medial temporal lobe structures (strong correlation with severity) <sup>29</sup>	Mild generalized cerebral cortical atrophy with minimal hippocampal atrophy and relative preservation of medial temporal lobe structures <sup>30</sup>
[18F]FDG PET	
Widespread metabolic deficits in neocortical association areas, with sparing of the basal ganglia, thalamus, cerebellum, primary sensory motor cortex, and visual cortex	Widespread cortical hypometabolism, more marked in primary visual and occipital association areas, and less severe in parietal, frontal, and anterior cingulate cortices. <sup>31</sup> Severe cholinergic deafferentation of the neocortex, particularly in posterior cortical regions <sup>32</sup>
Single photon emission computed tomography	
Parietotemporal hypoperfusion	Occipital hypoperfusion
123I-FP-CIT SPECT (DaT scan)	
No significant loss of DaT	Low nigrostriatal terminal density of DaT caused by severe nigrostriatal degeneration <sup>16</sup>
Myocardial scintigraphy with MIBG	
No significant change in MIBG uptake	Decreased MIBG uptake <sup>33</sup>
123I-FP-CIT: 123I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)nortropine; DaT: dopamine transporter; FDG PET: [18F]-fluoro-d-glucose positron emission tomography; MIBG: metaiodobenzylguanidine; SPECT: single photon emission computed tomography	

### Clinical Point

Compared with AD patients, DLB patients are at higher risk of developing extrapyramidal symptoms

as are depression and anxiety.<sup>1</sup> Agitation or aggressive behavior tends to occur late in the illness, if at all.

The causes of psychotic symptoms in DLB are not fully understood, but dopamine dysfunction likely is involved in hallucinations, delusions, and agitation, and serotonin dysfunction may be associated with depression and anxiety. Rapid eye movement (REM) sleep/wakefulness dysregulation, in which the dream imagery of REM sleep may occur during wakefulness, also has been proposed as a mechanism for visual hallucinations in DLB.<sup>22</sup> In DLB, psychotic symptoms occur early and are a hallmark of this illness, whereas in AD they usually occur in the middle to late stages of the disease.

**Motor symptoms.** In AD, extrapyramidal symptoms (EPS) are common later in the disease, are strongly correlated with disease severity, and are a strong, independent predictor of depression severity.<sup>23</sup> EPS are more common in DLB than in AD<sup>24</sup> and DLB patients are at higher risk of developing EPS even with low doses of typical antipsychotics, compared with AD patients.<sup>25</sup>

**Other symptoms.** REM sleep behavior disorder (RBD) is characterized by enacting dreams—often violent—during REM sleep. RBD is common in DLB and many patients also have excessive daytime somnolence. Other sleep disorders in DLB include insomnia, obstructive sleep apnea, central sleep apnea, restless legs

See this article at  
[CurrentPsychiatry.com](https://www.currentpsychiatry.com)  
for an overview of  
pharmacotherapy options  
for AD and DLB



## Differentiating dementias

### Clinical Point

REM sleep behavior disorder, characterized by enacting often violent dreams, is common in dementia with Lewy bodies

syndrome, and periodic limb movements during sleep.

In AD patients, common sleep behaviors include confusion in the early evening (“sundowning”) and frequent nighttime awakenings, often accompanied by wandering.<sup>26</sup> Orthostatic hypotension, impotence, urinary incontinence, and constipation are common in DLB. Lack of insight concerning personal cognitive, mood, and behavioral state is highly prevalent in AD patients and more common than in DLB.

### Diagnostic evaluation

Because there are no definitive clinical markers for DLB, diagnosis is based on a detailed clinical and family history from the patient and a reliable informant, as well as a physical, neurologic, and mental status examination that looks for associated noncognitive symptoms, and neuropsychological evaluation. Reasons DLB may be misdiagnosed include:

- Some “core” clinical features of DLB may not appear or may overlap with AD.
- Presence and severity of concurrent AD pathology in DLB may modify the clinical presentation, with decreased rates of hallucinations and parkinsonism and increased neurofibrillary tangles.
- Failure to reliably identify fluctuations—variations in cognition and arousal, such as periods of unresponsiveness while awake (“zoning out”), excessive daytime somnolence, and disorganized speech.<sup>27</sup>

Detecting and characterizing cognitive deficits in dementia patients using neuropsychological testing is important in establishing a clinical diagnosis, determining baseline levels of impairment, forming a prognosis, and initiating disease-specific treatments. Differences in neuropsychological findings in AD and DLB are outlined in *Table 2* (page 25).<sup>16,28-33</sup> Several studies have suggested using these measures to differentiate patients with DLB from those with AD.<sup>20</sup>

Evidence is insufficient to support using electroencephalographic and polysomnographic studies when initially evaluating patients with dementia. Brain CT or MRI are recommended as part of the initial

evaluation of dementia patients to exclude treatable causes of dementia and help clarify the differential diagnosis. Occipital hypometabolism and hypoperfusion demonstrated on PET and SPECT imaging have high sensitivity and specificity for differentiating AD from DLB.

To diagnose DLB more consistently, look for core features of the disease, RBD, antipsychotic hypersensitivity, and decreased striatal binding at presynaptic DaT sites.<sup>15</sup> Abnormal (low binding) DaT activity is the most reliable diagnostic marker for DLB.<sup>34</sup> Myocardial scintigraphy with MIBG is sensitive to pathologic changes of DLB before clinical expression and could overcome the difficulties of using clinical criteria alone to identify patients with DLB.<sup>35</sup> MIBG scintigraphy may be preferred to DaT scan because it is less expensive and its sensitivity and specificity to DLB are independent of the presence of parkinsonism.<sup>35</sup>

For an overview of pharmacotherapy options for patients with AD or DLB, see this article at [CurrentPsychiatry.com](http://CurrentPsychiatry.com).

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## Related Resources

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## Drug Brand Names

Aripiprazole • Abilify	Levodopa • Dopar, Larodopa
Clonazepam • Klonopin	Memantine • Namenda
Donepezil • Aricept	Quetiapine • Seroquel
Galantamine • Razadyne,	Rivastigmine • Exelon
Reminyl	

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## Bottom Line

Alzheimer's disease and dementia with Lewy bodies are the 2 most common causes of neurodegenerative dementia. Cerebrospinal fluid biomarkers and newer brain imaging techniques, including positron emission topography and single photon emission computed tomography, are increasingly used for differentiating the 2 diseases, but a detailed clinical history and comprehensive assessment of neuropsychological functions are of greatest value.

## Clinical Point

Hypoperfusion and occipital hypometabolism seen on imaging studies have high sensitivity for distinguishing AD from DLB

## Neuropathology of AD and DLB: A comparison

Alzheimer's disease (AD) is characterized by neuronal atrophy, synapse loss, and abnormal accumulation of amyloid-beta (A $\beta$ ) protein as senile plaques and hyperphosphorylated tau protein as neurofibrillary tangles (NFT). In most cases, NFT initially are found in medial temporal lobe structures (eg, the hippocampus and entorhinal cortex) and then extend to temporal, parietal, and frontal lobe association areas as the disease progresses. A $\beta$  deposition in AD begins in the parietal, temporal, and frontal association areas. Primary sensory and motor cortices and most subcortical structures are relatively spared until late in the disease process. Degeneration in basal forebrain structures results in a major reduction of cortical, limbic, and hippocampal cholinergic projections. Up to 50% of AD patients exhibit aggregation of alpha-synuclein into Lewy bodies. The presence of Lewy body pathology in AD is associated with a more aggressive disease course and accelerated cognitive dysfunction.<sup>a</sup>

The defining microscopic feature of dementia with Lewy bodies (DLB) is the Lewy bodies and Lewy neurites (LN), the pathologic aggregation of alpha-synuclein within the cytoplasm of neurons. Lewy bodies in the amygdala have been found in AD and other neurodegenerative

disorders but are far less likely to be associated with clinical manifestations than Lewy bodies found in the limbic cortex or neocortex. Recent studies have shown that patients with substantial NFT pathology are less likely to show clinical features of coexisting Lewy body pathology, and the clearest DLB clinical phenotype occurs in patients with relatively few tangles. A biologic relationship may exist between amyloid deposition and Lewy body formation. For example,  $\geq 30\%$  of patients with early-onset familial AD have Lewy bodies in addition to AD pathology, and the amount and distribution of insoluble A $\beta$  in patients with advanced DLB is comparable with that in AD.<sup>b,c</sup>

Biochemical studies of DLB show the involvement of dopaminergic neurons of the substantia nigra, which results in decreased dopamine in the basal ganglia. The brains of patients with DLB often have severe deficits in the acetylcholine biosynthetic enzyme choline acetyltransferase, which corresponds to neuronal loss in the nucleus basalis of Meynert. In AD, the neurons in the basal nucleus contain NFT, whereas in DLB the same population of neurons is vulnerable to Lewy bodies. In patients with concomitant AD and DLB, both NFT and Lewy bodies are found in the basal nucleus.

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## Differentiating dementias

### Box 2

## Treatments for Alzheimer's disease and dementia with Lewy bodies

**P**harmacotherapy options for patients with Alzheimer's disease (AD) or dementia with Lewy bodies (DLB) include cholinesterase inhibitors, memantine, antipsychotics, and other agents.

**Cholinesterase inhibitors.** Donepezil, rivastigmine, and galantamine are FDA-approved for treating AD. Their efficacy appears to be similar, so the choice of agent is based largely on cost, patient tolerability, and physician experience.

No medications are FDA-approved for treating DLB. Neocortical cholinergic activity assessed by choline acetyltransferase levels is more severely depleted in DLB than in AD, and this deficit is correlated with the presence of visual hallucinations and global severity of cognitive impairment.<sup>a</sup> Therefore, drugs that enhance central cholinergic function offer a therapeutic approach for DLB; cognitive and hallucinatory symptoms are the anticipated targets. Multiple anecdotal reports, open-label studies,<sup>b,c</sup> and 1 randomized, placebo-controlled trial<sup>d</sup> suggest that cholinesterase inhibitors are efficacious in DLB, with reported benefits in cognition, fluctuations, psychotic symptoms, and parkinsonian symptoms. A 20-week randomized, double-blind, placebo-controlled multicenter study<sup>d</sup> of patients with DLB found rivastigmine, 6 to 12 mg/d, was superior to placebo. Patients receiving rivastigmine exhibited significantly reduced anxiety, delusions, and hallucinations and significantly better performance on a computerized battery of neuropsychological tests, especially tasks that required sustained attention. Differences between rivastigmine and placebo disappeared after drug discontinuation.

**Memantine** is a noncompetitive antagonist of *N*-methyl-D-aspartate receptors that is effective in AD.<sup>e</sup> The possible involvement of glutamate in DLB has provided a rationale for treating DLB with memantine. Two randomized controlled trials in DLB found that patients treated with memantine for 24 weeks performed better on Clinical Global Impression of Change, but not on most other secondary outcome measures.<sup>f,g</sup> In both studies, memantine was well tolerated. However, other studies have noted worsening of delusions and hallucinations with memantine in DLB patients.<sup>h</sup>

**Antipsychotics.** Agitation is common in moderate and advanced AD. Atypical antipsychotics have been used with variable efficacy to treat agitation, but their use is associated with excess mortality. DLB patients

pose a considerable therapeutic challenge because antipsychotics—the mainstay of treatment of psychosis and behavioral problems in most other disorders—can provoke severe, irreversible, and often fatal sensitivity reactions in this type of dementia.<sup>i</sup> A 2- to 3-fold increased mortality risk associated with antipsychotic sensitivity reactions in DLB is partly mediated via acute blockade of postsynaptic dopamine D2 receptors in the striatum. For severe and disabling psychosis, a trial of a cholinesterase inhibitor and/or lowering the dose of antiparkinsonian medication should be considered first. In urgent situations, small doses of an atypical antipsychotic that is least associated with parkinsonism side effects—such as quetiapine or aripiprazole—should be used.

**Other treatments.** Treatment of parkinsonian symptoms in DLB patients is similar to that for Parkinson's disease, but the risk of psychotic symptoms in DLB warrants a conservative approach. Levodopa seems to be more effective than dopamine agonists and produces fewer side effects.<sup>j</sup> Rapid eye movement sleep behavior disorder often responds to low doses of clonazepam (0.25 to 1.5 mg). Depression and anxiety disorders are common in AD at all stages and their treatment is not fundamentally different than in geriatric patients without dementia. Selective serotonin reuptake inhibitors and electroconvulsive therapy have been used successfully in depressed patients with AD or DLB.<sup>k,l</sup>

**Disease-modifying treatments.** Researchers are evaluating an array of anti-amyloid and neuroprotective therapeutic approaches for AD based on the hypothesis that amyloid-beta protein plays a pivotal role in disease onset and progression. Interventions that reduce amyloid production, limit aggregation, or increase clearance may block the cascade of events comprising AD pathogenesis. Reducing tau hyperphosphorylation, limiting oxidation and excitotoxicity, and controlling inflammation also may be beneficial strategies. Potentially neuroprotective and restorative treatments such as neurotrophins, neurotrophic factor enhancers, and stem cell-related approaches also are being investigated.

There are no large-scale studies of disease-modifying treatments for DLB. Potential areas of research include the relationship between proteasome function and  $\alpha$ -synuclein pathology, the role of beta-synuclein, and the impact of alterations to alpha-synuclein on its propensity to aggregate.

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