**SUMMARY**

**Background:** Dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD) are the two most common types of dementing neurodegenerative disease after Alzheimer’s disease (AD). Both of these conditions are often diagnosed late or not at all.

**Methods:** Selective literature review.

**Results:** The severe cholinergic and dopaminergic deficits that are present in both DLB and PDD produce not only motor manifestations, but also cognitive deficits, mainly in the executive and visual-constructive areas, as well as psychotic manifestations such as visual hallucinations, delusions, and agitation. The intensity of these manifestations can fluctuate markedly over the course of the day, particularly in DLB. Useful tests for differential diagnosis include magnetic resonance imaging and electroencephalography; in case of clinical uncertainty, nuclear medical procedures and cerebrospinal fluid analysis can be helpful as well. Neuropathological studies have revealed progressive alpha-synuclein aggregation in affected areas of the brain. In DLB, beta-amyloid abnormalities are often seen as well. Neuropathological studies have revealed progressive alpha-synuclein aggregation in affected areas of the brain. In DLB, beta-amyloid abnormalities are often seen as well.

**Conclusion:** DLB should be included in the differential diagnosis of early dementia. If motor manifestations arise within one year (DLB), dopaminergic treatment should be initiated. On the other hand, patients with Parkinson’s disease should undergo early screening for signs of dementia so that further diagnostic and therapeutic steps can be taken in timely fashion, as indicated. Cholinesterase inhibitors are useful for the treatment of cognitive deficits and experiential/behavioral disturbances in both DLB (off-label indication) and PDD (approved indication).

The question of whether dementia is an inevitable fate for many of us as we grow older cannot be answered with a simple “yes” or “no.” Old age is the most important risk factor for the development of any dementia. The older the mean age of a population, the greater the total number of people with dementia. In Germany, 6.5% to 8.7% of the population older than 65 years and 30% of those older than 89 are affected by one of the different types of dementia. Even if the incidence of dementia remains stable, the number of those affected in Germany will about double by 2050, owing to the aging population alone.

Neurodegenerative changes are the most common causes for dementia (for example, Alzheimer’s disease [AD]), followed by microangiopathies or macroangiopathies. Patients with such vascular cerebral changes often show additional and relevant neurodegenerative changes at postmortem (e1).

In the past decades, further, relatively common subcategories of neurogenerative dementias have been defined, clinically as well as neuropathologically. These include dementia with Lewy bodies (DLB)—the occurrence of dementia before Parkinson’s syndrome—and Parkinson’s disease dementia (PDD). Because these types of dementia respond to treatment with cholinesterase inhibitors, and because of the serious side effects associated with administration of traditional neuroleptic drugs, it’s important to distinguish these from Alzheimer’s dementia. The diagnostic certainty of the medical diagnosis of dementia is still low, at 78% to 84%; especially the certainty in diagnosing Lewy body dementia is low (e2). This may be due to the overlap of symptoms with the symptoms of Alzheimer’s disease, but it may also be due to lacking awareness of these disease entities among doctors.

The diagnostic evaluation and treatment of Lewy body dementia and Parkinson’s disease dementia require notably higher resources per patient than in Alzheimer’s disease (2). The probable reason for this is the combination of cognitive and physical impairments in the former dementia types. Both DLB and PDD also lead to a reduced quality of life for patients and an increased psychological burden for the relatives and carers compared with Alzheimer’s disease (2, e3).
Epidemiology
Like Alzheimer’s disease, dementia with Lewy bodies is a common neurodegenerative type of dementia. According to different studies, the estimated prevalence of DLB among all dementias is 3.6% to 6.6% in people older than 65 and 1.7% to 30.5% in dementia patients older than 65; these findings depend on the study design (3).

Parkinson’s disease itself is one of the more common diseases of old age; its prevalence is 1.8% in people older than 65. Compared with the general population, Parkinson’s patients have a sixfold increased risk of developing dementia (4, e4). According to a systematic review, the prevalence of Parkinson’s disease dementia is 0.5% in those older than 65 in the general population and 3.6% in dementia patients (e5). However, the data on Parkinson’s disease dementia are subject to great variation—namely, 39.9% (e6) to up to 80% after a mean disease course of 8 years (e7).

Risk factors for developing Parkinson’s disease dementia include hallucinations early on in the disease course and the akinetic-rigid type of Parkinson’s disease. Old age, comorbid depression, and nicotine misuse are also risk factors (e4).

Clinical symptoms
The main symptoms in Parkinson’s disease dementia include impaired executive functioning, impairments to visual-spatial functioning, cognitive deficits, and lack of drive that are mostly due to impaired memory function. In terms of memory, patients with Parkinson’s disease dementia are primarily affected by impaired strategic encoding and recall. Executive functions are the processes that are necessary to control behaviors and plan action. In addition to the dopaminergic system, further neurotransmitters of the central nervous system are essential for these deficits to develop, especially acetylcholine, noradrenalin, and serotonin (5).

Clinical course
The symptoms of dementia with Lewy bodies start with cognitive and/or further psychiatric impairments and are accompanied within the first year (or from the beginning) by the typical symptoms of Parkinson’s syndrome. In Parkinson’s disease dementia, cognitive deficits and/or dementia develop only if the full motor symptoms of Parkinson’s have been present for a minimum of one year (‘one year rule’ for clinical studies). If full-blown disease is present then usually no differences between the two disease entities exist, neither clinically nor neuropathologically.

Clinical classification criteria
Clinical classification criteria for dementia with Lewy bodies were first defined by a group of experts around McKeith in 1995 and revised in 1999 and 2005. The specificity of these criteria is 95%; their sensitivity is very low, at 32%, which is due to the overlap of clinical symptoms with those of Alzheimer’s disease, among

<table>
<thead>
<tr>
<th>BOX 1 Clinical-diagnostic consensus criteria for dementia with Lewy bodies (DLB)*1</th>
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<tbody>
<tr>
<td><strong>Central characteristic</strong></td>
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<tr>
<td>- Dementia with impairments in everyday functioning and often well functioning memory at onset of illness</td>
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<td><strong>Key characteristics are</strong></td>
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<td>- Fluctuating cognition (especially attention and awareness/alertness)</td>
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<td>- Visual hallucinations</td>
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<td>- Symptoms of Parkinson’s disease</td>
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<td><strong>Highly suggestive characteristics are</strong></td>
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<td>- REM sleep behavior disorder</td>
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<td>- Pronounced oversensitivity to neuroleptics</td>
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<td>- Reduced dopaminergic activity in the basal ganglia (on SPECT or PET scan)</td>
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<td><strong>For a diagnosis of “possible” DLB</strong></td>
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<tr>
<td>- Central characteristic AND</td>
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<tr>
<td>- at least one key characteristic or at least a strongly suggestive characteristic</td>
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<tr>
<td><strong>For a diagnosis of “likely” DLB</strong></td>
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<tr>
<td>- Central characteristic AND</td>
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<tr>
<td>- at least two key characteristics or one key characteristic together with one strongly suggestive characteristic</td>
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<tr>
<td><strong>Supporting characteristics (these are often present, but they currently have no diagnostic specificity)</strong></td>
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<td>- Repeated falls or episodes of syncope, transient impairment of consciousness, severe autonomic dysfunction (orthostatic hypotension, urinary incontinence), hallucinations in other modalities, systematic delusions, depression, an intact medial temporal lobe (cranial CT, cranial MRI scan), reduced metabolism, measured on SPECT/PET scan, especially in the occipital lobe, pathological MIBG-SPECT scan of the myocardium, slowed down EEG activity with intermittent temporal sharp waves</td>
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<tr>
<td><strong>Findings that do not support DLB</strong></td>
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<td>- Cerebrovascular lesions on cranial CT or cranial MRI or focal-neurological symptoms</td>
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<tr>
<td>- Other disorders that may provide a satisfactory explanation for the clinical symptoms</td>
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<tr>
<td>- Spontaneous symptoms of Parkinson’s disease which occur exclusively in severe dementia</td>
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</table>

*1 Modified (from McKeith et al, 19–21); SPECT, single photon emission computed tomography; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; MIBG-SPECT, 13-iodine metaiodobenzylguanidine single photon emission computed tomography; EEG, electroencephalography
For a diagnosis of "possible" Parkinson's disease dementia

- Queen Square Brain Bank criteria \(^2\) for Parkinson's disease
- Dementia with:
  - Impairments in more than one cognitive domain
  - Reduced cognition compared with the premorbid level
  - Deficit related impairments in everyday functioning

Associated clinical characteristics are \(^2\)
- Attention
- Executive functions
- Visual-spatial functions
- Memory
- Speech
- Apathy
- Personality changes and mood changes
- Hallucinations
- Delusions
- Increased daytime fatigue

Characteristics that are indicative of different circumstances/disorders as the cause of mental impairment \(^4\)
- Cognitive and behavioral symptoms only in combination with, for example, acute confusion in systemic illness, adverse effects from medication
- Major depression according to the DSM-IV
- Characteristics that are consistent with a suspected diagnosis of "probable vascular dementia"

For a diagnosis of "likely" Parkinson's disease dementia
1. Both key characteristics
2. Confirmed deficits in at least 2 of the 4 domains mentioned under \(^2\)
3. None of the criteria listed under \(^3\) is fulfilled
4. None of the characteristics listed under \(^4\) is present
   - The presence of at least one of the behavioral symptoms listed under \(^2\) supports the diagnosis

For a diagnosis of "possible" Parkinson's disease dementia
1. Both key characteristics
2. \(^2\) does not apply—for example, motor or sensorimotor aphasia or exclusive impairment of memory (memory function does not improve after help has been given or in recognition) while attentiveness remains, behavioral symptoms may be present or not, OR
3. one or more criteria listed under \(^2\) are met
4. none of the criteria listed under \(^4\) is met

\(^1\) Modified from \(^22\)
\(^2\) Clinical criteria for a diagnosis of Parkinson's disease according to which, in addition to the absence of exclusion criteria (such as no improvement after levodopa), the presence of supporting criteria (for example, unilateral onset), bradykinesia, and at least one of the following symptoms have to be present: muscle rigidity, resting tremor, and/or postural instability (e21)

Characteristics that are consistent with a suspected diagnosis of "probable vascular dementia"
- Presence of other abnormalities that may cause cognitive impairments (for example, a finding of relevant vascular lesions)
- The time interval between the development of motor and cognitive symptoms is not known

Characteristics that make a diagnosis of Parkinson's disease dementia unlikely
- Deficit related impairments in everyday functioning
- Reduced cognition compared with the premorbid level
- Impairments in more than one cognitive domain
- Executive functions
- Attention
- Autonomic disturbances

Additional investigations
Neuropsychological tests
Patients who have dementia with Lewy bodies or Parkinson's disease dementia display frontal-executive and visual-constructive deficits in both groups. The latter can be demonstrated particularly poignantly by means of the "clock drawing test"; the patients are asked to complete the pre-drawn circle of a clock face to show 10 minutes past 11 o’clock (Figure 1 a–c).

Both dementias also have in common the fluctuating neuropsychological deficits. These are also responsible for the fact that cognitive impairments are usually not diagnosed by performing simple, global screening procedures, such as the mini-mental state examination (MMSE), only once.

Imaging
For reasons of differential diagnostic evaluation, cerebral imaging (preferably cranial magnetic resonance imaging [MRI]) should be undertaken in patients with Lewy body dementia and Parkinson's disease dementia, to exclude structural changes and possible additional vascular lesions. Electroencephalography (EEG) is also recommended, to rule out an epilepsy related cause (e9). Patients with Lewy body dementia usually have slower EEG rhythms at baseline than patients with Alzheimer’s disease or Parkinson's disease dementia (e10).

In dementia with Lewy bodies—by contrast to Alzheimer’s disease—a dopaminergic nigrostriatal deficit leads to the characteristic visual hallucinations (e7).
is present. Nuclear medical investigation to determine dopamine transporter binding are appropriate—for example, by means of FP-CIT SPECT (single photon emission computed tomography) scanning, to distinguish dementia with Lewy bodies (in the absence of comorbid Parkinson’s syndrome) from Alzheimer’s disease (sensitivity 78% and specificity 90%) (9). Szentigraphy of the myocardium can be used to show the sympathetic denervation of the heart in dementia with Lewy bodies and Parkinson’s disease dementia (e11). Nuclear medical techniques can also help in establishing the distinction to Alzheimer’s disease.

Analyzing cerebrospinal fluid (CSF) for beta-amyloid(1–42) and tau protein also helps in differentiating dementia with Lewy bodies from Alzheimer’s disease: in dementia with Lewy bodies, the tau protein measurement is mostly normal—except in some cases with an unusually rapid disease course—and beta-amyloid(1–42) is lowered (as in Alzheimer’s disease) (10, e12). For tau protein, the sensitivity and specificity for a diagnosis of Alzheimer’s disease versus dementia with Lewy bodies are 73% and 76%, respectively (e12). A normal finding on CSF analysis, however, rules out neither dementia with Lewy bodies nor Parkinson’s disease dementia.

Nuclear medical investigations and, in individual cases, CSF analysis should be considered in cases that are not clear on differential diagnostic evaluation.

The role of alpha-synuclein

Many neurodegenerative disorders are characterized by pathological protein aggregates in particularly vulnerable neural populations, which may result in the clinically characteristic disease symptoms—such as memory loss and Parkinson’s symptoms. Parkinson’s disease dementia and dementia with Lewy bodies have pathomorphological structures that mainly consist of the protein alpha-synuclein (Figure 2).

Treatment

Treatment of motor symptoms in Parkinson’s disease

Treatment of motor, psychological/psychiatric, and autonomous symptoms of Parkinson’s disease should be symptomatic, depending on the degree of clinical impairment and independently of a diagnosis of dementia with Lewy bodies or Parkinson’s disease dementia. Attention needs to be paid to the reduced response of motor symptoms, especially akinesis, to levodopa in 40% of patients with Lewy body dementia. Owing to the development of the dementia and the tendency to develop psychoses in dementia with Lewy bodies, monotherapy with levodopa is usually recommended. Studies of combination treatment with dopamine agonists and levodopa have not been conducted in patients with Lewy body dementia; whether combination treatment with dopamine agonists is useful and tolerable depends on the individual case. This requires consideration, especially bearing in mind the patient’s age (11). Close monitoring for possible psychotic symptoms is urgently advised. The administration of anticholinergic drugs is contraindicated.

Therapy for dementia

Patients with Lewy body dementia or Parkinson’s disease dementia have a pronounced cholinergic deficit. Acetylcholine is broken down in the brain by acetylcholinesterase and butyrylcholinesterase. Cholinesterase inhibitors (ChEI) inhibit different isoenzymes of the cholinesterases and increase the concentration of acetylcholine (which, owing to the disease, is low) in

Figure 1: Clock drawing tests from three patients

a) Male, age 73 years, diagnosis: dementia with Lewy bodies, MMSE score of 18 points
b) Male, age 80 years, diagnosis: Parkinson’s disease dementia, MMSE score: 25 points
c) Male, age 74 years, diagnosis Parkinson’s disease dementia, MMSE score: 20 points

MMSE, mini-mental state examination
ChEI are effective in treating cognitive symptoms in dementia with Lewy bodies and Parkinson’s disease dementia. Additionally they reduce neuropsychiatric symptoms. By 2009, the only drug that was licensed in Germany for the treatment of Parkinson's disease dementia was rivastigmine by oral administration (capsules); currently, no ChEI are licensed for dementia with Lewy bodies.

By contrast to other ChEI that are licensed for the treatment of Alzheimer’s disease, rivastigmine inhibits not only isoenzymes of acetylcholinesterase but also those of butyrylcholinesterase. No clinical advantage of this principle of dual effectiveness has been shown. In a randomized, double-blind, placebo controlled, multicenter study of 541 patients with Parkinson's disease dementia, the group that received treatment with an average of 8.6 mg of rivastigmine per day showed slight improvements in cognitive functioning, by 2.1 points in a scale of 0–70 of the ADAS-cog (a subtest of the Alzheimer's disease assessment scale). The patients who had been treated with placebo underwent a slight deterioration, of a mean of 0.7 points. A clinically noticeable improvement was noted in 19.8% of patients who were treated with rivastigmine, but also in 14.5% of patients who had received placebo. 13% and 23.1%, however, deteriorated (P=0.007) (12). These values are mean group values of almost all therapeutic studies and do not mean that each single patient would have improved or, if given placebo, deteriorated. The extent to which cognitive improvements relevant for everyday life can be deduced for the individual case (or not) remains to be seen from longer studies investigating therapy over a longer term. In particular, the duration of treatment with rivastigmine in Parkinson's disease dementia has not been studied under controlled conditions.

Adverse effects for rivastigmine (>5%) include nausea, vomiting, tremor, diarrhea, falls, vertigo/dizziness, and hypotension; rarely, hallucinations have been reported (4.7%).

Improved cognitive functioning has been shown for donepezil in patients with Parkinson's disease dementia in few controlled trials with small case numbers, some of which were methodologically unsatisfactory (e13–e15).

Similar effects were shown for patients with Lewy body dementia, mainly in terms of a reduction in neuropsychiatric symptoms, especially hallucinations and productive-delusional symptoms (13, e16, e17). Formally, the use of rivastigmine and other ChEI in dementia with Lewy bodies is off-label in Germany. The use (even as an off-label treatment) of other antidementia drugs is not justified on the basis of current data. According to a comparative study, no differences in effectiveness exist for the 3 ChEI (rivastigmine, galantamine, and donepezil) in the treatment of Lewy body dementia if studies are of a comparable quality and size (e18).

Figure 2: Histology in dementia
a) alpha-synuclein aggregates in the cortex of patients with Lewy body dementia can be shown in the shape of Lewy bodies by using conventional histological techniques; Bar=50 µm (HE, arrow, inset).
b) The cortical Lewy bodies are not as compact as those within the substantia nigra and can be visualized easily by using immunohistochemical techniques (antibodies 4B12 [Abcam]; red reaction product, blue counter stain, arrow).
c) More than 90% of alpha-synuclein aggregates do not form Lewy bodies. Using one of the modern molecular pathological methods (PET blot), small alpha-synuclein aggregates in the synapses of cortical nerve cells can be shown as a dark reaction product. Bars=100 µm. Used: paraffin embedded tissue blot (PET-blot) as view from above without microscopic enlargement. PET-blot, antibody 4B12, same enlargement as b) (e20) (image provided by PD Dr Walter J Schulz-Schaeffer, Department of Neuropathology, University Medical Center Göttingen, Germany)
In principle, cognition can be improved clinically noticeable and objectively by ChEI; often, everyday functioning is also improved, with fewer neuropsychiatric symptoms.

The question of how long treatment with ChEI should be continued is not unproblematic in view of the costs incurred and is currently the subject of critical discussion. In any case, the treatment should be controlled and evaluated 6 months after treatment initiation (this is also in accordance with the S3 guideline on dementia [14]). Cessation of treatment with ChEI should be decided on an individual as well as clinical basis. In case of progressive dementia and an MMSE score of less than 10 in spite of ChEI, the treatment needs to be questioned because no license exists in this scenario in Germany. Caution is indicated in abrupt cessation of treatment with ChEI because this entails the risk of substantial cognitive deterioration (15).

Treatment of hallucinations, delusions, and agitation

Visual hallucinations, delusions, and other productive-psychotic symptoms may occur early on in the disease course in dementia with Lewy bodies. In Parkinson’s disease, these often develop only during the course of the disease, and in a scenario where new hallucinations or psychoses occur for the first time after a change in medication, the most recent change in medication should be reversed (11). If this does not yield the desired success or if hallucinations occur without prior change of medication, the medication for Parkinson’s disease should be changed according to the treatment algorithm provided in the guidelines (Figure 3).

If this does not improve the productive-psychotic symptoms to a satisfactory degree, the use of antipsychotics may be considered. This is particularly the case when (especially in patients with Parkinson’s disease) a reduction in the Parkinson medication is followed by a substantial deterioration in motor functioning, so that a minimum dose of levodopa is a definite requirement.

It is in particular the productive-psychotic symptoms of dementia with Lewy bodies and Parkinson’s disease dementia that place a heavy burden on relatives and carers; they are also responsible for a multitude of admissions to residential care homes, so that medication treatment is absolutely essential.

The raised sensitivity or intolerability of dementia with Lewy bodies vis-à-vis the typical antipsychotic drugs has been described repeatedly (16). By contrast, severe side effects in reaction to the atypical antipsychotic drug quetiapine (daily dosage 12.5–100 mg/d to a maximum of 200–300 mg/d) and clozapine (daily dosage 12.5–100 mg/d) have rarely been observed. Larger studies are lacking, and future studies should distinguish between dementia with Lewy bodies and Parkinson’s disease dementia. In a comparative study of 40 patients with Parkinson’s disease, both the group receiving quetiapine (mean dosage: 91 mg/day) and the group receiving clozapine (mean dosage: 26 mg/day) showed improvements of their psychotic symptoms.
without a deterioration of their Parkinson’s symptoms (e19). Rarely, the anticholinergic side effects increase confusion. It is important to start treatment with a very low dose—for example, 6.25 mg or 12.5 mg clozapine. Because of the risk of agranulocytosis during clozapine treatment, regular blood counts are essential. Other atypical antipsychotics are not recommended, and typical antipsychotics should not be used in patients with dementia with Lewy bodies and Parkinson’s disease dementia owing to their greater sensitivity to neuroleptic drugs. Especially treatment with typical neuroleptic drugs may increase the symptoms of Parkinson’s disease to a life threatening degree (to the extent of an aki- netic crisis with massive swallowing impairment), to an impaired conscious level, and autonomic dysfunction, to the extent of a malignant neuroleptic syndrome with high mortality (16).

In acute situations, patients may be given a short course of clomethiazole and lorazepam (for the purpose of sedation) (17).

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**Conflict of interest statement**

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**References**


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REVIEW ARTICLE

Lewy Body and Parkinsonian Dementia
Common, but Often Misdiagnosed Conditions

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eReferences