

# Chapter 7

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## Dementia with Lewy bodies

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## What are the diagnostic criteria and key points for early diagnosis of dementia with Lewy bodies (DLB)?

### Answer

For clinical diagnosis of DLB, the revised diagnostic criteria of the DLB International Workshop are used. The diagnostic criteria for DLB are also provided in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Memory impairment may not be noticeable in the early stage of the disease. The key point for early diagnosis is to look for the presence or absence of decline of cognitive functions other than memory (such as attention, executive function, and visuospatial cognition), REM sleep behavior disorder, parkinsonism, autonomic symptoms, olfactory disturbance, depressive symptoms, and other symptoms.

In June 2017, new DLB diagnostic criteria were published.



### Comments and evidence

In 1995, the first DLB International Workshop proposed the term “dementia with Lewy bodies” (DLB) and its clinical diagnostic criteria<sup>1)</sup>. The diagnostic criteria were revised at the third workshop, and further revised in 2017<sup>2)</sup>. Probable DLB (almost definite) can be diagnosed if two or more of the core features are present. In the presence of only one core clinical feature, probable DLB can also be diagnosed if one or more of the indicative biomarkers are present. The DSM-5 published in 2013 shows the diagnostic criteria for major neurocognitive disorder (dementia) with Lewy bodies and mild neurocognitive disorder (mild cognitive impairment) with Lewy bodies<sup>3)</sup>.

In DLB, since memory impairment is often unremarkable in the early stage of the disease, it is important to examine whether there are disorders other than memory impairment, such as attention disorder, impaired executive function, and visuospatial impairment. Moreover, diverse clinical symptoms may manifest in addition to cognitive impairment. Paying attention to these clinical symptoms provides important clues for early diagnosis of DLB. REM sleep behavior disorder is often seen from the prodromal stage<sup>4)</sup>. Furthermore, studies that compared early and prodromal stages of DLB with those of Alzheimer’s disease have reported that parkinsonism<sup>4-6)</sup>, gait disorder<sup>6)</sup>, autonomic symptoms<sup>4, 7)</sup>, olfactory dysfunction<sup>4, 7)</sup>, hallucinations<sup>4-6)</sup>, delirium<sup>5, 6)</sup>, sleep disturbance and psychiatric symptoms<sup>7)</sup> occur more frequently in DLB. Since many factors such as hypersensitivity to antipsychotic drugs, syncope, and falls are directly related to poor prognosis in DLB, an accurate diagnosis from the early stage is important for appropriate disease management.

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### Search formula

PubMed search: July 5, 2015 (Sunday), August 18, 2015 (Tuesday)

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## What are the clinical and pathological differences between dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD)?

### Answer

(1) Lewy body disease (LBD) is a disease concept that includes all the diseases containing Lewy bodies from the pathological aspects. (2) There is no evidence that there is fundamental difference between DLB and PDD. DLB and PDD can be viewed as a disease spectrum called LBD. (3) As an operational criterion used in research, it has been proposed to diagnose DLB when dementia precedes parkinsonism, and PDD when parkinsonism precedes dementia for one year or longer.

### Comments and evidence

#### 1. Terminology issue of DLB and PDD

At the first DLB International Workshop in 1995, the term DLB was proposed for dementia characterized by the neuropathological feature of the appearance of Lewy bodies with  $\alpha$ -synuclein as the main component<sup>1)</sup>. On the other hand, if dementia occurs after the onset of motor symptoms of Parkinson's disease (PD), this condition has been called "Parkinson's disease with dementia (PDD)". In the International Workshop, PDD is defined as cases in which parkinsonism has been present for one year or longer before the onset of dementia, and DLB as cases in which the onset of dementia is before the onset of parkinsonism or within one year after onset of parkinsonism (1 year rule)<sup>1)</sup>. This one-year rule continues to be adopted subsequently in the third workshop<sup>2)</sup>. However, note that this rule is only an operational criterion used in research.

#### 2. Similarities and differences between DLB and PDD

A conference held in 2006 which examined the boundary issues between PDD and DLB concluded that "the differing temporal sequence of symptoms and clinical features of PDD and DLB justify distinguishing these disorders. However, a single Lewy body disorder model was deemed more useful for studying disease pathogenesis because abnormal neuronal  $\alpha$ -synuclein inclusions are the defining pathologic process common to both PDD and DLB"<sup>3)</sup>. The diagnostic criteria for PDD have also been proposed<sup>4)</sup>.

Lewy bodies containing  $\alpha$ -synuclein as the major component are frequently found in neurons of the brain and in autonomic nervous system. According to the distribution pattern, Lewy body disorder is classified into the diffuse type (neocortical type), limbic type, brainstem type, and cerebral type (Lewy bodies are scarcely seen in the brainstem). Many patients with LBD also have concomitant pathology of Alzheimer's disease, and are classified into Alzheimer type, usual type, and pure type (in decremental order of concomitant Alzheimer's pathology). Lewy body pathology spreads in different patterns, including spread from the medulla oblongata ascending to the cerebral cortex, progression from the amygdala to cerebral cortex or brainstem, and descending spread from the cerebral cortex to brainstem. Such pathological diversity probably accounts for the broad spectrum of LBD phenotypes.

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- 1) McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology*. 1996; 47(5): 1113-1124.
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## What are the characteristic laboratory and imaging biomarker of dementia with Lewy bodies (DLB)?

### Answer

DLB is characterized by reduced uptake on dopamine transporter scintigraphy and metaiodobenzylguanidine (MIBG) myocardial scintigraphy. On CT/MRI, the medial temporal lobe is relatively preserved. Cerebral SPECT and FDG-PET show decreased blood flow and glucose metabolism in the occipital lobe.

A

### Comments and evidence

In DLB, decreased uptake is observed on  $^{123}\text{I}$ -MIBG myocardial scintigraphy and dopamine transporter scintigraphy. In particular,  $^{123}\text{I}$ -MIBG myocardial scintigraphy is useful for differentiation from other parkinsonism-related diseases (such as multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration)<sup>1)</sup>, while dopamine transporter scintigraphy is highly useful for differentiation from Alzheimer's disease<sup>2)</sup>. A report shows that a combination of  $^{123}\text{I}$ -MIBG myocardial scintigraphy and dopamine transporter scintigraphy can differentiate DLB from Alzheimer's disease dementia with 96.1% sensitivity and 90.7% specificity<sup>3)</sup>.

When using dopamine transporter (DAT) scintigraphy in diagnosis, careful attention has to be given to the following.

- (1) Differentiation between DLB and other parkinsonism-related diseases (including progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration) is difficult because both are presynaptic disorders of nigrostriatal dopaminergic neurons.
- (2) Vascular parkinsonism shows normal to mild loss in DAT uptake in the striatum. Drug-induced parkinsonism shows normal findings, but it is necessary to confirm the history of the causative drugs use such as anti-dopaminergic agents.
- (3) Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and other drugs (drugs with stimulant effect such as cocaine, amphetamine, methylphenidate, and modafinil) affect the imaging result because of interaction of the ligand with drugs that have mechanisms of action on dopamine transporters and serotonin transporters. Therefore, suspending medication or using alternative drugs should be considered before examination. Anti-parkinsonian drugs such as cholinesterase inhibitors, levodopa and MAOB inhibitors have little effects on the results<sup>4)</sup>.
- (4) Pregnant women and persons who are allergic to excitatory substances such as cocaine are general contraindications. Breastfeeding is a relative contraindication<sup>4)</sup>.
- (5) For patients with liver dysfunction, alcohol hypersensitivity, urinary disorder, or allergic constitution, the examination has to be administered with caution and after obtaining consent.

The hippocampus and parahippocampal gyrus are relatively preserved on brain MRI, but brainstem atrophy may be diagnosed by statistical analysis such as Voxel-based Specific Regional Analysis System for Alzheimer's Disease (VSRAD)<sup>5)</sup>. On cerebral blood flow scintigraphy, both Alzheimer's disease and DLB show decreased blood flow in the occipital lobe, posterior cingulate gyrus, and precuneus. Whereas hippocampal blood flow is reduced in Alzheimer's disease, it is relatively preserved in DLB. Compared to Alzheimer's disease, DLB is also characterized by showing earlier decreases in blood flow and metabolism in the primary visual cortex<sup>6)</sup>. Study has shown that if the diagnosis of DLB is difficult by brain SPECT alone, combining with  $^{123}\text{I}$ -MIBG myocardial scintigraphy increases the diagnostic accuracy<sup>7)</sup>.

In summary, characteristic abnormalities for DLB are found in  $^{123}\text{I}$ -MIBG myocardial scintigraphy, dopamine transporter scintigraphy, MRI combined with VSRAD, and cerebral blood flow scintigraphy. When diagnosis is difficult using a single examination, a combination of multiple examinations is expected to increase diagnostic accuracy.

Furthermore, while amyloid PET shows increased uptake in DLB similar to that in Alzheimer's disease, cholinesterase-PET (ChE-PET) is known to demonstrate decreased ChE uptake mainly in the occipital lobe in DLB<sup>8)</sup>.

Regarding cerebrospinal fluid (CSF) biomarkers, there are many reports of low CSF  $\alpha$ -synuclein levels in DLB as in Parkinson's disease, but the usefulness of this marker has not been established. A report has shown that CSF levels of phosphorylated  $\alpha$ -synuclein and  $\alpha$ -synuclein oligomers are elevated in DLB as in Parkinson's disease<sup>9)</sup>. In addition, low CSF A $\beta$ 42 level has been reported in DLB compared to controls<sup>10)</sup>.

New diagnostic criteria for DLB have been published in June 2017 (see CQ7-1). Among these criteria, the following

indicative biomarkers have been added: (1) reduced uptake in basal ganglia demonstrated by dopamine transporter scintigraphy; (2) reduced uptake on <sup>123</sup>I-MIBG myocardial scintigraphy; and (3) REM sleep without atonia (RWA) confirmed by polysomnography (PSG). In particular, abnormal muscle tone during REM sleep is a highly specific phenomenon for patients with Lewy body pathology, and is recognized as an important sign even if the other biomarkers are negative.

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## What are the clinical course and prognosis of dementia with Lewy bodies (DLB)?

### Answer

Reports have indicated that there is no difference in the progression of cognitive impairment between DLB and Alzheimer's disease. There are reports indicating that the time from initial consultation or diagnosis to hospital admission or death is shorter in patients with DLB.



### Comments and evidence

Several studies have compared the clinical course and prognosis of DLB and Alzheimer's disease. Many of them report no differences between DLB and Alzheimer's disease in terms of progression of cognitive impairment<sup>1-6</sup> and progression of declined functional abilities<sup>1,2</sup>. The result of a recent meta-analysis also confirms no difference in the progression of cognitive impairment<sup>7</sup>. On the other hand, there are reports showing that the DLB group has a shorter time from the first hospital visit to end point (admission to institutional, admission to hospital, or death)<sup>6</sup>, and a shorter survival duration from onset of dementia<sup>5,8</sup> or from diagnosis<sup>9</sup>. In any case, careful attention should be paid to the complications such as pneumonia, which worsen the outcome.

### References

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## What is the treatment strategy planned for dementia with Lewy bodies (DLB)?

### Answer

Regarding treatment strategy for DLB, symptomatic treatment for each of the diverse clinical symptoms is recommended. The strategy should include pharmacotherapy and non-pharmacological therapies. A

### Comments and evidence

DLB may manifest diverse symptoms including cognitive impairment, hallucinations, delusion, depressive symptoms, apathy, abnormal REM sleep behavior and other behavioral and psychological symptoms of dementia (BPSD), extrapyramidal symptoms, and autonomic symptoms. Because of the diversity of symptoms, it is important to determine the major symptoms that should be the target of treatment, and then plan the treatment strategy.

Since DLB has high risk of drug-induced adverse events, non-pharmacological interventions such as care and environmental adaptation are particularly important. While donepezil has been used for treating cognitive impairment, symptomatic drugs should be used for BPSD, motor deficits, and autonomic dysfunction <sup>1)</sup>.

### References

- 1) McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005; 65(12): 1863-1872.

### Search formula

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#1 (Lewy body disease/TH OR Lewy body disease/TI) AND (Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiologic treatment)OR Treatment/TH OR Treatment/TI OR Therapy/TI)

## Are there any drugs for the treatment of cognitive impairment in dementia with Lewy bodies (DLB)?

### Recommendation

Cholinesterase inhibitors have been reported to be effective for cognitive impairment in DLB patients.

1B

### Comments and evidence

The usefulness of cholinesterase inhibitors for cognitive impairment in DLB has been reported<sup>1)</sup>. In Japan, donepezil (Aricept®) is covered by health insurance for the treatment of cognitive impairment in DLB. In a meta-analysis of randomized controlled trials (RCT), both cholinesterase inhibitors and memantine are safe and improve Clinician's Global Impression of Change (CGIC), but only cholinesterase inhibitors enhance cognitive function<sup>1)</sup>. According to the results of a meta-analysis in 2015 analyzing 17 large-scale studies on Lewy body disease, cholinesterase inhibitors are useful in improving cognitive function without worsening motor function<sup>2)</sup>.

#### 1. Cholinesterase inhibitor (ChEI)

##### a. Donepezil

Four open-label trials have shown the efficacy of donepezil in improving cognitive function in DLB patients. In Japan, a randomized controlled trial showed that oral donepezil at doses of 5 mg and 10 mg improved Mini Mental State Examination (MMSE) and Neuropsychiatric Inventory (NPI)-2 scores (hallucination and cognitive function)<sup>3)</sup>. Although there was no significant difference in NPI-10 score, effectiveness was observed in change of dementia symptoms. Improvement in caregiver's burden was also found in the high-dose (10 mg) group. Furthermore, in a multicenter open label long-term study (52 weeks), change in cognitive function and improvement of NPI-4 score were also observed<sup>4)</sup> [See CQ7-7 for details of the effects of donepezil on BPSD). Subsequently, a 56-week long-term study confirmed the tolerability and maintenance of cognitive function improvement in patients treated with donepezil 5 mg and 10 mg<sup>5)</sup>. A placebo-controlled double-blind study (phase III) in DLB patients demonstrated improvement in MMSE score with 10 mg, but not with 5 mg of donepezil<sup>6)</sup>.

On the other hand, a randomized controlled trial has shown the effectiveness of donepezil for cognitive function also in PDD<sup>7)</sup>.

##### b. Rivastigmine

In a RCT conducted in patients with DLB, although the improvements of MMSE score and global clinical evaluation were not significant in patients treated with oral rivastigmine, the effect of improving attention was particularly remarkable<sup>8)</sup>. A RCT of rivastigmine in patients with PDD has shown significant improvement in multiple cognitive function evaluation tests including the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog)<sup>9)</sup>. Regarding the efficacy on cognitive impairment in PDD, rivastigmine was highly recommended by the European Federation of Neurological Society (EFNS) (clinical evidence class I, recommended level A) and American Academy of Neurology (AAN) (evidence level class II, recommendation level B)<sup>10)</sup>.

##### c. Galantamine

A 24-week open-label study of galantamine in DLB patients showed improvement in global clinical impression and in cognitive function (ADAS-cog)<sup>11)</sup>.

#### 2. NMDA receptor antagonist: memantine

A 24-week placebo-controlled RCT of memantine in 72 DLB or PDD patients showed improvement in a cognitive function test requiring attention (A Quick Test of Cognitive Speed; AQT) and in CGIC<sup>12)</sup>. However, the results of a meta-analysis on memantine for Lewy body disorders reported by Matsunaga et al.<sup>13)</sup> showed no significant improvement in cognitive function.

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#1 ("Lewy Body Disease" [Mesh] OR Lewy body disease\* OR "Lewy body dementia" OR "dementia with Lewy body") AND ("Cognition Disorders/therapy" [Mesh] OR ((cognition disorder\* OR cognitive disorder\*) AND (therapy OR therapeutic OR treatment))) OR ("Lewy Body Disease/drug therapy" [Majr] OR ("Lewy body" [TI] OR "Lewy bodies" [TI]) AND (donepezil OR rivastigmine)) OR ("Dementia/drug therapy" [Majr] AND "Parkinson Disease/complications" [Mesh])) AND ("Cognition/drug effects" [Majr] OR ((cognitive function\* OR cognitive assessment\* OR cognitive subscale\*) AND improve\*))

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#1 (Lewy body disease/TH OR Lewy body disease /TI) AND (Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI ) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiologic treatment)OR Treatment/TH OR Treatment/TI OR Therapy/TI)

## Are there any treatments for behavioral and psychological symptoms of dementia (BPSD) and REM sleep behavior disorder (RBD) in dementia with Lewy bodies (DLB)?

### Recommendation

(1) Although *Yokukansan* and atypical antipsychotics have been reported to be therapeutic drugs for BPSD, sufficient consideration for safety is required. (2) The effectiveness of clonazepam for RBD has been reported. Some case reports have indicated that *Yokukansan*, ramelteon, and donepezil are effective when clonazepam cannot be used. 2C

### Comments and evidence

Patients with DLB may show hypersensitivity to antipsychotic drugs. Therefore, non-pharmacological interventions should take priority over pharmacotherapy for the treatment of BPSD. Donepezil, a therapeutic drug for cognitive impairment in DLB, may also be effective against BPSD<sup>1)</sup>.

If there is no response to the above interventions, symptomatic drugs for BPSD are used. *Yokukansan* has been shown to be effective in improving NPI total score, hallucinations, delusion, depression, and anxiety symptoms<sup>2)</sup>. Although *Yokukansan* does not cause extrapyramidal symptoms or anticholinergic symptoms, hypokalemia may occur occasionally which requires attention. In addition, a report indicates the effectiveness of memantine against BPSD such as delusion, hallucinations, abnormal nocturnal behaviors, and abnormal appetite in patients with DLB<sup>3)</sup>. Antipsychotics have been used for BPSD in DLB. However, as noted above, patients with DLB may have hypersensitivity to antipsychotics; therefore use of these drugs requires special caution<sup>4)</sup>. Haloperidol is contraindicated for Parkinson's disease, and should also be avoided in patients with DLB in principle.

Among atypical antipsychotics, quetiapine and aripiprazole that have mild adverse effects on the extrapyramidal system are considered to be relatively safe<sup>4)</sup>, but there is little evidence. Although there are reports on the effectiveness of atypical antipsychotics for BPSD in DLB, discontinuation due to adverse effects is not uncommon. When using these drugs, it is necessary to use the minimum dose and always pay attention to the occurrence of adverse events.

Clonazepam has been reported to be effective for the treatment for RBD. However, special attention should be paid to over-sedation and falls when used in patients with DLB. Case reports have indicated that *Yokukansan*<sup>5)</sup>, ramelteon<sup>6)</sup>, and donepezil<sup>7)</sup> were effective when clonazepam cannot be used due to adverse effects. There is little evidence for the effect of clonazepam on insomnia in DLB. In patients with DLB, attention should be paid to the effects of sleep medications causing dizziness, falls and hang-over. Two cases of insomnia in DLB responding to ramelteon have been reported<sup>8)</sup>. A report also indicates the effectiveness of *Yokukansan* in improving total time and efficiency of sleep, and reducing the number of arousals during sleep<sup>9)</sup>.

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## ■ Search formula

PubMed search: July 5, 2015 (Sunday), August 18, 2015 (Tuesday)

#1 ("Lewy Body Disease" [Mesh] OR Lewy body disease\* OR "Lewy body dementia" OR "dementia with Lewy body") AND (("behavioral psychological symptom dementia" OR BPSD) AND (therapy OR therapeutic OR treatment)) OR "Behavioral Symptoms/therapy" [Mesh] OR (("REM sleep" OR sleep disorder\*) AND (therapy OR therapeutic OR treatment)) OR "Sleep Disorders/therapy"[Mesh]) OR (((("Lewy Body Disease/psychology" [Mesh] OR ((("Lewy body" [TI] OR "Lewy bodies" [TI]) AND dementia[TI]) AND (mental impairment\* OR behavioural symptom\* [TI]))) AND ("Lewy Body Disease/drug therapy" [Majr] OR "Delusions/drug therapy" [Majr] OR "Psychotic Disorders/drug therapy" [Majr] OR ("Dementia/drug therapy" [Majr] AND "Dementia/psychology" [Mesh]))) OR ("REM Sleep Behavior Disorder/drug therapy" [Majr] OR ("REM Sleep Behavior Disorder/drug therapy" [Mesh] AND "REM Sleep Behavior Disorder/physiopathology"[Mesh]))) AND ("Nootropic Agents" [Mesh] OR "Antipsychotic Agents" [Mesh] OR "Drugs, Chinese Herbal" [Mesh] OR "Dibenzothiazepines" [Mesh] OR "Anticonvulsants" [Mesh] OR "Clonazepam" [Mesh] OR "Cholinesterase Inhibitors" [Mesh]))

Ichushi search: July 6, 2015 (Monday)

#1 (Lewy body disease/TH OR Lewy body disease/TI) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiologic treatment) OR Treatment/TH OR Treatment/TI OR Therapy/TI) AND (Behavioral psychological symptoms /TH OR Behavioral psychological symptoms/TI OR Behavioral symptoms /TH OR Behavioral symptoms /TI OR Psychiatric symptoms/TH OR Psychiatric symptoms/TI OR Sleep disorder/TH OR Sleep disorder/TI)

## Are there any treatments for autonomic symptoms (such as orthostatic hypotension, constipation, sweating, urination disorder) in dementia with Lewy bodies (DLB)?

### Recommendation

For autonomic symptoms in DLB, drugs for the treatment of autonomic symptoms in Parkinson's disease (PD) are used while paying attention to deterioration of cognitive function and psychiatric symptoms. Non-pharmacological therapies are also used.

2C

### Comments and evidence

There are no randomized controlled trials (RCT) for autonomic symptoms in DLB, but treatments for orthostatic hypotension, constipation, abnormal sweating, and urinary disorder are given according to those used for the treatment of these conditions in PD<sup>1)</sup>. In a study of 29 patients with DLB, urinary incontinence (97%) and constipation (83%) were the most common, while hypotension was found in 66%, and a history of syncope in 28%<sup>2)</sup>.

Not only orthostatic hypotension, but postprandial hypotension also occurs frequently. Especially in older patients, dehydration is a common triggering factor, which requires attention. For the treatment of orthostatic hypotension, apart from non-pharmacological interventions such as salt intake, head-up tilt in bed, and wearing compressive stockings<sup>3)</sup>, pharmacotherapy using droxidopa, midodrine, and fludrocortisone is effective.

For constipation, adequate dietary fiber and water intake, and use of laxatives such as magnesium oxide, lubiprostone, senna, sennoside, and *Daikenchuto* are useful. In addition, prescribe mosapride and domperidone to improve gastrointestinal peristalsis. In DLB, pay attention to paralytic ileus as in PD.

Regarding urinary disorder in DLB, avoid using anticholinergic drugs as far as possible because these drugs may deteriorate cognitive function. Oxybutynin should not be used because this drug readily passes into the central nervous system and its anticholinergic action on the central nervous system has the risk of worsening cognitive impairment<sup>4)</sup>. Paroxetine, a selective serotonin reuptake inhibitor (SSRI), and milnacipran, a serotonin-norepinephrine reuptake inhibitor (SNRI), are sometimes useful. Donepezil has been reported to improve attention in patients with dementia, and at the same time suppress the micturition reflex via central muscarinic M2 receptor<sup>5)</sup>. Use of the adrenoceptor antagonists such as urapidil, tamsulosin, and naftopidil may be considered in cases of difficulty in urination due to enlarged prostate.

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### Search formula

PubMed search: July 5, 2015 (Sunday), August 18, 2015 (Tuesday)

#1 ("Lewy Body Disease" [Mesh] OR Lewy body disease\* OR "Lewy body dementia" OR "dementia with Lewy body") AND ("Autonomic Nervous System Diseases/therapy" [Mesh] OR "Constipation/therapy" [Mesh] OR "Hyperhidrosis/ therapy" [Mesh] OR "Dysuria/therapy" [Mesh] OR ((autonomic dysfunction\* OR orthostatic hypotension\* OR constipation\* OR hyperhidrosis OR dysuria) AND (therapy OR therapeutic OR treatment))) OR ("Parkinson Disease/therapy" [Majr] OR Parkinson's disease\*) AND (((orthostatic hypotension\* OR GI symptom\* OR GI complaint\*) AND improve\*) OR "Urination Disorders/drug therapy" [Majr] OR "Urinary Bladder Diseases/drug therapy" [Majr])

Ichushi search: July 6, 2015 (Monday)

#1 (Lewy body disease/TH OR Lewy body disease/TI OR Lewy body disease/TI) AND (Autonomic nervous system disease/TH OR Autonomic nervous system disease/TI OR Autonomic nervous symptom/TI OR orthostatic hypotension/TI OR Constipation/TH OR Constipation/TI OR Hyperhidrosis/TH OR Hyperhidrosis/TI OR Sweating/TI OR Urination disorder/TH OR Urination/TI)

## What are the suitable treatments for parkinsonism in dementia with Lewy bodies (DLB)?

### Recommendation

Levodopa is recommended for parkinsonism in DLB patients, but high doses should be avoided because of the risk of worsening psychiatric symptoms and involuntary movements (such as dyskinesia). Use of dopamine agonist tends to worsen psychiatric symptoms, and therefore require special caution.

2C

### Comments and evidence

Although there is no randomized controlled trial (RCT) for the treatment of parkinsonism in patients with DLB, levodopa is recommended according to the recommendation for Parkinson's disease (PD)<sup>1,2</sup>. However, response to levodopa in DLB is generally inferior to that in PD<sup>2</sup>. Note that high doses should not be used because there is little benefit in improving motor symptoms, while there is a risk of exacerbating psychiatric symptoms. When levodopa is used, start from a low dose and up-titrate gradually to the minimally required dose. Anticholinergic drugs such as trihexyphenidyl have the risk of impairing cognitive function and should be avoided in principle<sup>2</sup>.

Using high-dose levodopa from the early stage tends to induce not only psychiatric symptoms such as hallucination, but also motor complications such as dyskinesia and wearing-off symptoms<sup>3</sup>. Therefore, start from a low dose and pay attention to whether psychiatric symptoms are worsened. Since psychiatric symptoms such as hallucination and impulse control disorder are easily induced in patients with DLB, dopamine agonists may be used with special caution<sup>4</sup>. In the case of difficulty with rolling over in bed due to wearing off symptoms at night or in early morning, rotigotine patch has been reported to be effective for the group of diseases causing atypical parkinsonism including PD with dementia<sup>5</sup>, but avoid using this drug if there is any deterioration in psychiatric symptoms such as hallucination.

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### Search formula

PubMed search: July 5, 2015 (Sunday), August 19, 2015 (Wednesday)

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#1 ("Lewy Body Disease" [Mesh] OR Lewy body disease* OR "Lewy body dementia" OR "dementia with Lewy body") AND ("Parkinsonian Disorders/therapy" [Mesh] OR "Neurologic Manifestations/therapy" [Mesh] OR((Parkinsonian disorder* OR Parkinsonism OR dyskinesia OR motor dysfunction*) AND (therapy OR therapeutic OR treatment))) OR ("Parkinson Disease/drug therapy" [Majr] OR ((Parkinson disease* [TIAB] OR Parkinson's disease*[TIAB]) AND (therapy [TIAB] OR intervention* [TIAB]))) AND ("Lewy Body Disease/drug therapy" [Mesh] OR ("Lewy body" [TI] OR "Lewy bodies" [TI]) AND dementia [TI] AND (therapy [TI] OR management[TI]))OR "Dyskinesias" [Majr] OR dyskinesia* [TI])
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Ichushi search: July 6, 2015 (Monday)

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#1 (Lewy body disease/TH OR Lewy body disease/TI) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiologic treatment)OR Treatment/TH OR Treatment/TI OR Therapy/TI) AND (Parkinsonism/TH OR Parkinsonism/TI OR Parkinson disease/TI OR Involuntary movement/TH OR Involuntary movement/TI OR Dyskinesia/TH OR Dyskinesia/TI)
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## What are the non-pharmacological interventions for dementia with Lewy bodies (DLB)?

### Answer

Non-pharmacological interventions are also important for DLB, and appropriate care and environmental adjustment are recommended.



### Comments and evidence

Non-pharmacological interventions such as appropriate care and environmental improvement are also important in the management of DLB. However, although non-pharmacological interventions may be effective in improving behavioral and psychological symptoms of dementia (BPSD) and functional abilities in patients with DLB, there are no research reports proving them so far. Since cognitive impairment and visual hallucination are worsened by decline in arousal and attention levels<sup>1)</sup>, social interaction and environmental stimulation may be effective. For BPSD in DLB, using a person-centered approach to improve caregiver's burden should be tried first<sup>2)</sup>. For dementia in general, removal of any trigger of agitation (pain, fear, hallucination, delusion, environment) is recommended<sup>3)</sup>. The results of a meta-analysis show that giving advice on care to caregivers, supporting caregivers, and acquiring stress management skills are effective to reduce BPSD<sup>4)</sup>, and these approaches may also be useful in patients with DLB. Parkinsonism is a risk of falls in DLB patients<sup>1, 5)</sup>. Although some reports have shown that gait rehabilitation training is useful as a non-pharmacological intervention for falls and gait disturbances in patients with Parkinson's disease, there is little evidence for DLB.

### References

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### Search formula

PubMed search: July 5, 2015 (Sunday), August 19, 2015 (Wednesday)

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#1 ("Lewy Body Disease/therapy" [Mesh] OR ((Lewy body disease* OR "Lewy body dementia" OR "dementia with Lewy body") AND (therapy OR therapeutic OR treatment OR rehabilitation OR intervention*))) AND ("Rehabilitation" [Mesh] OR rehabilitation* OR "Psychotherapy" [Mesh] OR "Social Support" [Mesh] OR psychosocial intervention*) OR (("Lewy Body Disease/therapy" [Mesh] OR ("Lewy body" [TI] OR "Lewy bodies" [TI]) AND dementia [TI] AND (therapy [TI] OR management [TI]))) AND (specific intervention* OR nonpharmacologic OR cognitive-behavioral intervention*) OR ("Dementia/therapy" [Majr] AND "Phototherapy" [Mesh])
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Ichushi search: July 6, 2015 (Monday)

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#1 (Lewy body disease/TH OR Lewy body disease/TI) AND ((SH = Rehabilitation)OR Rehabilitation/TH OR Rehabilitation/TI OR Psychological therapy/TH OR Psychological therapy/TI OR Psychotherapy/TI OR Psychosocial therapy/TI OR Psychosocial intervention/TI OR Social support/TH OR Social support/TI)
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