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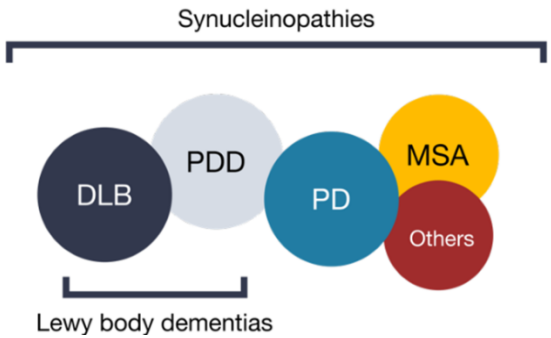


Lewy Body Dementia;

Dementia with Lewy bodies (DLB) & Parkinson's Disease Dementia (PDD)

July 19, 2024

CHA Bundang Medical Center

Hyun Sook Kim, MD, PhD

Terminologies

Lewy body disease, pathological finding of Lewy bodies (aggregated α-synuclein inclusions in neurons) on postmortem examination

Lewy body dementia (LBD), an umbrella term including both DLB and PDD

The second-most common degenerative dementia after AD; DLB is only one part of this diagnostic umbrella

Dementia with Lewy bodies (DLB), also categorized as both an ‘atypical parkinsonism’ and an ‘Alzheimer-disease related dementia’ (ADRD)

Individuals with AD dementia and co-existing Lewy bodies,

Lewy body variant of Alzheimer disease, clinically diagnosed and pathologically confirmed AD with concomitant Lewy bodies on pathology (~1990s)

dual pathological diagnosis (AD + LBD) or AD with Lewy bodies when insufficient to meet formal DLB pathological criteria

Therapeutic Advances in Neurological Disorders. 2021;14

Current concepts and controversies of PDD and DLB

In PD, the cardinal pathological features are of degeneration of dopaminergic cells in the nigrostriatal system, and by widespread intracytoplasmic Lewy bodies (LBs) and Lewy neurites (LNs), the main component of which is α-synuclein.

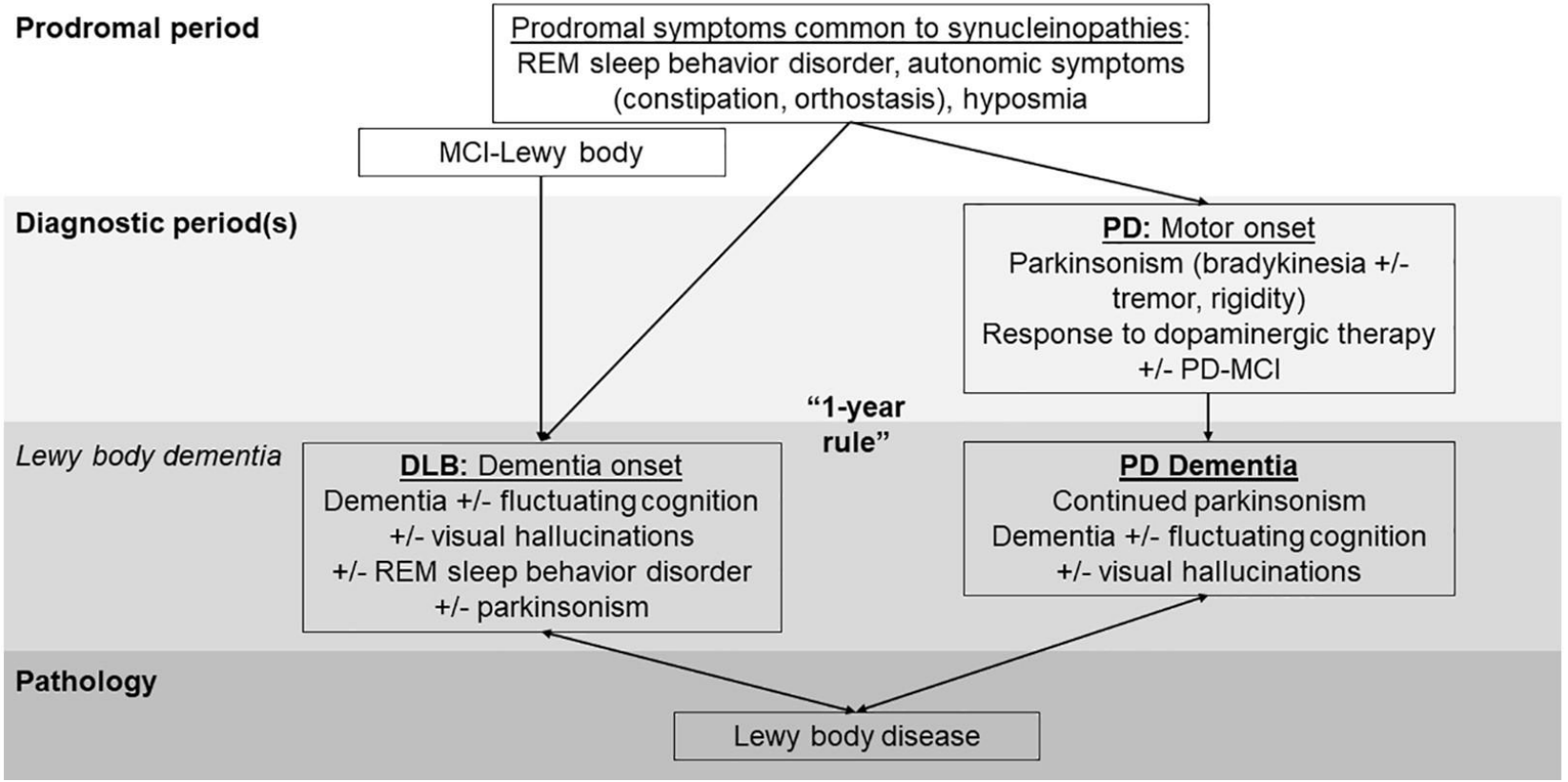
Neuropathologically, PDD and DLB are difficult to differentiate; a **higher prevalence of amyloid co-pathology (and related imaging findings) in DLB** than PDD.

*In PD, a wide range of non-motor features, including cognitive impairment; subtle cognitive impairment (common at the point of diagnosis) or **PDD (as high as 70% after 10 yrs of symptom)***

*In DLB, cognitive impairment precedes or coincides with the development of parkinsonian signs by (arbitrary) **one year**.*

F1000Research 2017, 6:1604
Therapeutic Advances in Neurological Disorders. 2021;14

Lewy body dementia over the clinical course



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Clinical criteria for PDD and DLB

	Dementia with Lewy bodies	Parkinson disease dementia
Essential features	Dementia before or <1 year after motor parkinsonism (attention, executive, visuospatial > memory, language)	Dementia in the setting of established Parkinson disease (>1 year) (attention, executive, visuospatial > memory, language)
Core features	Cognitive fluctuations Visual hallucinations Spontaneous parkinsonism (>1 feature) Rapid eye movement (REM) sleep behavior disorder	
Associated/ suggestive features	Severe neuroleptic sensitivity Postural instability Repeated falls Syncope/transient loss of consciousness Autonomic dysfunction Depression Hallucinations in other modalities Systematized delusions	Apathy Depression/anxiety Hallucinations Delusions Excessive daytime sleepiness
Indicative biomarkers	Low dopamine transporter uptake Reduced scintigraphy cardiac metaiodobenzylguanidine uptake Sleep study–confirmed REM sleep behavior disorder	Not applicable

- clinical features included in diagnostic criteria of both DLB and PDD
- known shared clinical features explicitly mentioned not in BOTH criteria
- differing clinical features of timing of dementia onset in the course of disease

CONTINUUM (MINNEAP MINN) 2022;28:1314–1332

	PD	PDD	DLB	AD
Cognitive deficits	**Rare and mild**	**Late**	**Early and typical**	
Dementia	None	Late	Typical	
Memory and attention	None	Variable		Prominent
Hallucinations and delirium	Rare	Typical		Occasional
Delusions	Occasional	Typical		
REM sleep disorder	Occasional	Typical		Rare
Parkinsonism	**First manifestation**		**Late or none**	**Rare**
Bradykinesia, Rigidity Gait and postural instability	Typical			Rare
Tremor	Typical		Variable	Rare

Disease-Modifying Targets in Neurodegenerative Disorders 2017, pages 175-198
BMC Medicine 2018, 16:34

Neuropsychological Comparison of DLB/PDD vs. AD

Alzheimer's affects language and memory, while **Parkinson's affects problem solving (executive function), speed of thinking**, memory and other cognitive functions, as well as mood.

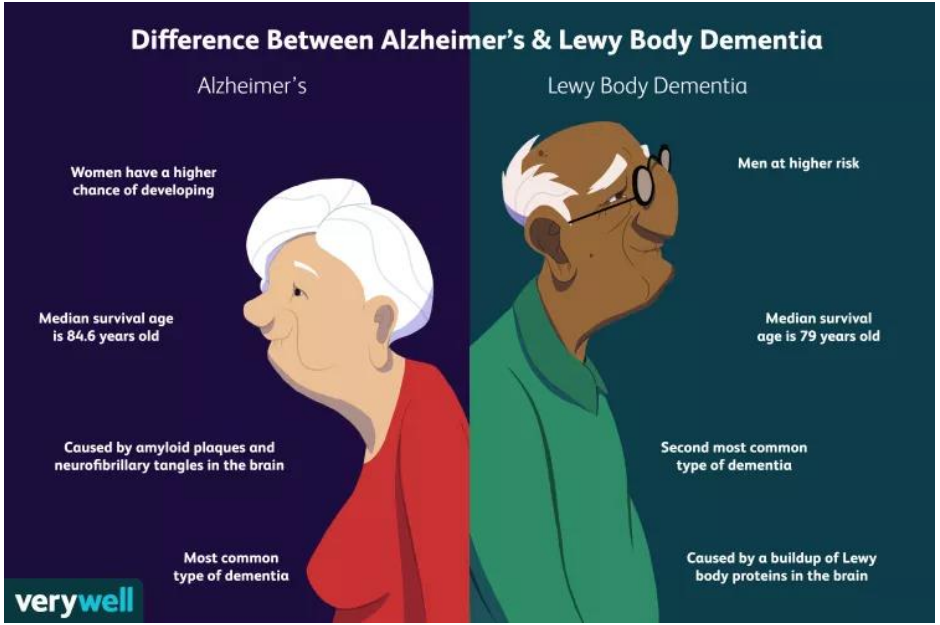
AD involves greater impairment of memory, especially verbal, probably related to greater temporal lobe pathology -> AD hallmarks: rapid rates of forgetting and intrusions

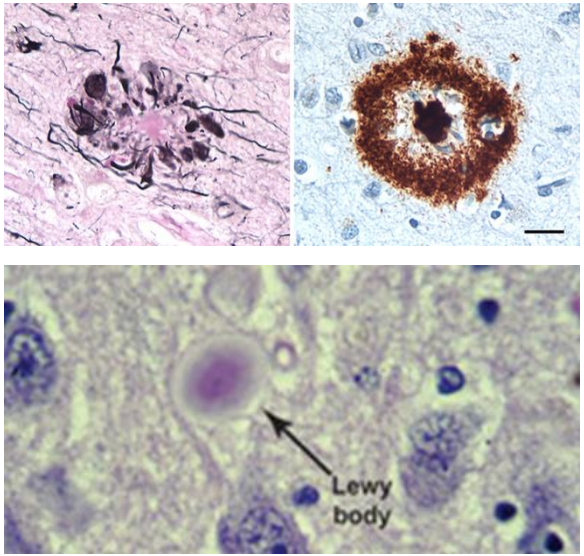
DLB involves greater visuoperceptual and constructional deficits, which may be linked to posterior cortical hypometabolism and visual hallucinations.

DLB/PDD perform worse than AD on complex attention tasks (Stroop, Trail making) but not on simple tasks (e.g., digit span).

DLB/PDD perform worse on executive function tasks (e.g., card sorting) than AD. Executive dysfunction linked to basal forebrain cholinergic deficits.

Language data more equivocal: same naming and fluency deficits in AD and DLB, worse naming in AD, worse letter fluency in DLB





Dementia With Lewy Bodies (DLB)

Prodromal DLB

Well established prodromal features of synucleinopathies; RBD/REM sleep without atonia, olfactory dysfunction, dysautonomia, and psychiatric disturbance (e.g. anxiety and depression)

Research criteria for prodromal DLB in 2020

three prodromal phenotypes: *MCI, delirium, and psychiatric -onset*

sufficient evidence only to propose diagnostic criteria for MCI-onset DLB, termed *MCI with Lewy bodies (MCI-LB)*

non-amnestic MCI (usually affecting attention, visuospatial/visuoperceptual function), particularly in the context of associated RBD, fluctuations, and/or subtle parkinsonism

Prodromal DLB

Numerous reports of provoked or unprovoked delirium as a presenting feature of DLB (***delirium-onset***), sometimes occurring in individuals without cognitive impairment and years before the DLB diagnosis

- unclear whether this reflects mistaking cognitive fluctuations for delirium or a greater vulnerability to delirium in individuals with prodromal DLB
- occurrence of delirium should prompt an assessment for other features that would suggest DLB and caution in antipsychotic use for the treatment of delirium (*Remind,* antipsychotic hypersensitivity in DLB)

Late-onset major depressive disorder and late-onset psychosis are potentially types of ***psychiatric-onset DLB***; difficult and unclear how to differentiate prodromal DLB from late-onset psychiatric disturbance unrelated to Lewy pathology

Pathology and co-pathology

multiple forms of Lewy pathology: diffuse (neocortical), transitional (limbic), brainstem-predominant, amygdala-predominant, or olfactory bulb only

pathologic findings evaluating both the degree of Lewy-related pathology and the amount of AD neuropathological change

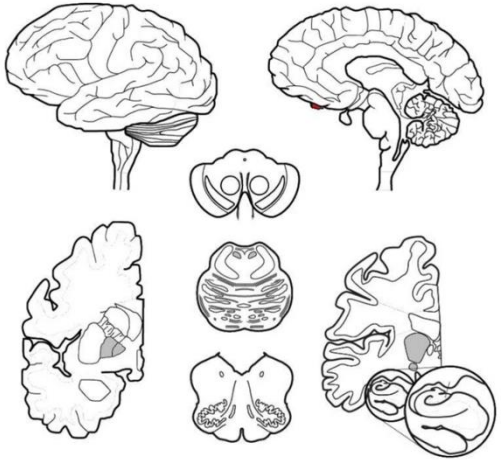
Half of all individuals with Lewy body disease have sufficient pathology for a secondary neuropathological diagnosis of AD at autopsy; a clinical diagnosis of DLB is highly likely when the distribution of α-synuclein pathology is greater than tau pathology.

The presence of AD pathology may also influence the presence of depression/dysphoria in DLB

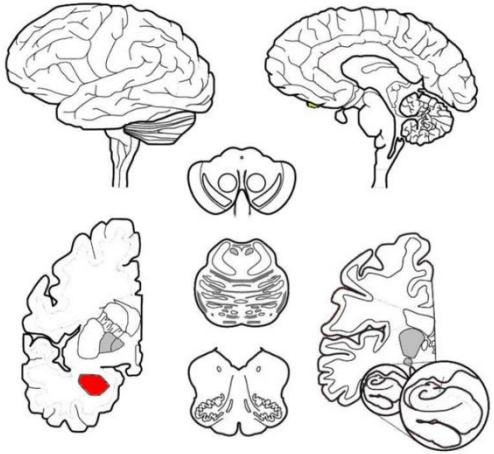
Lewy Pathology Consensus Criteria (LPC)

Category of LP	OB	Amy.	dmX or SN (1)	MTL or Cing. (1)	Fr. or Pa. ctx (1)
Olfactory only	+	-	-	-	-
Amygdala predominant	- / +	+	-	-	-
Brainstem predominant	- / +	- / +	+	-	-
Limbic	- / +	- /+	- / +	+	-
Neocortical	- / +	- / +	- / +	- /+	+

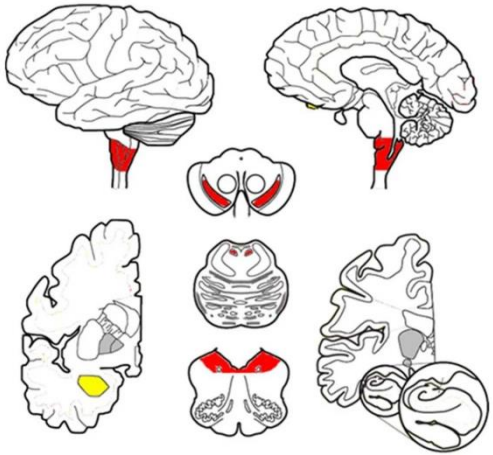
Olfactory only



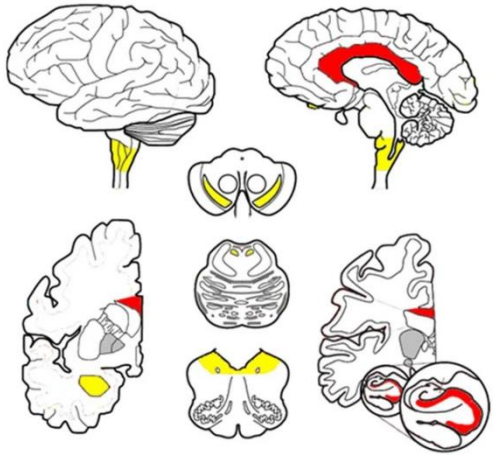
Amygdala predominant



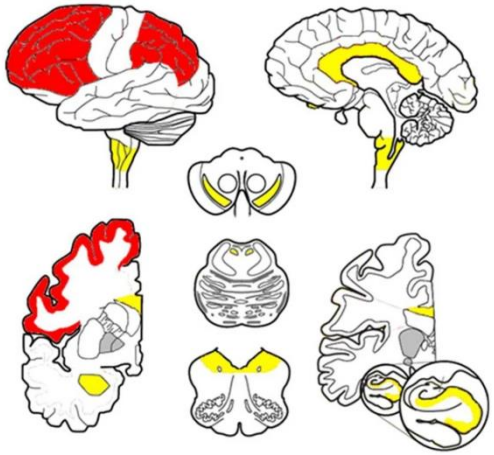
Brainstem predominant



Limbic



Neocortical



Acta Neuropathol 141, 159–172 (2021)

Table 1. Criteria for the clinical diagnosis DLB from the fourth consensus report of the DLB Consortium (2017)..

Probable DLB:

(1) *Required criterion*: Dementia, usually with prominent and early impairments in attention, executive function, and visuoperceptual ability (memory involvement more with progression)

(2) Presence of ⩾2 core clinical features (± indicative biomarker) ***OR*** 1 core clinical feature + ⩾1 indicative biomarker(s)

Possible DLB:

(1) *Required criterion*: Dementia, usually with prominent and early impairments in attention, executive function, and visuoperceptual ability (memory involvement more with progression)

(2) Presence of 1 core clinical feature (no indicative biomarker) ***OR*** ⩾1 indicative biomarker(s) (no core clinical features)

Core clinical features:

1. Fluctuating cognition with pronounced variations in alertness and attention
2. Recurrent visual hallucinations
3. REM sleep behavior disorder
4. Parkinsonism (presence of one or more of: bradykinesia, rest tremor, rigidity)

Indicative biomarkers:

1. Reduced basal ganglia dopamine transporter uptake (SPECT or PET)
2. Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy
3. Polysomnographic confirmation of REM sleep without atonia

Source: Adapted from McKeith *et al.*[6]

DLB, dementia with Lewy bodies; MIBG, metaiodobenzylguanidine; PET, positron emission tomography; REM, rapid eye movement; SPECT, single-photon emission computed tomography.

The criteria also include supportive clinical features and biomarkers that are helpful in diagnosing DLB but are not formally part of the criteria (see text). If parkinsonism is present, the dementia should have started first or within 1 year of motor symptom onset for a diagnosis of DLB (the 'one year rule'). If parkinsonism is the only core clinical feature and appears only in the context of severe dementia, DLB is less likely.

Therapeutic Advances in Neurological Disorders. 2021;14

Table 2. Research criteria for the diagnosis of mild cognitive impairment with Lewy bodies (2020)..

Probable MCI-LB:

(1) *Required criterion*: Mild cognitive impairment as defined by the presence of: (1) subjective cognitive complaint (from patient, informant, or clinician), (2) impairment in 1 or more domains (typically attention-executive or visual processing), ***AND*** (3) preserved or minimally affected independence in functional abilities

(2) Presence of ⩾2 core clinical features (± indicative biomarker) ***OR*** 1 core clinical feature + ⩾1 indicative biomarker(s)

Possible MCI-LB:

(1) *Required criterion*: Mild cognitive impairment as defined by the presence of: (1) subjective cognitive complaint (from patient, informant, or clinician), (2) impairment in 1 or more domains (typically attention-executive or visual processing), ***AND*** (3) preserved or minimally affected independence in functional abilities

(2) Presence of 1 core clinical feature (no indicative biomarker) ***OR*** ⩾ 1 indicative biomarkers (no core clinical features)

Core clinical features:

1. Fluctuating cognition with variations in alertness and attention
2. Recurrent visual hallucinations
3. REM sleep behavior disorder
4. Parkinsonism (presence of one or more of: bradykinesia, rest tremor, rigidity)

Proposed biomarkers:

1. Reduced basal ganglia dopamine transporter uptake (SPECT or PET)
2. Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy
3. Polysomnographic confirmation of REM sleep without atonia

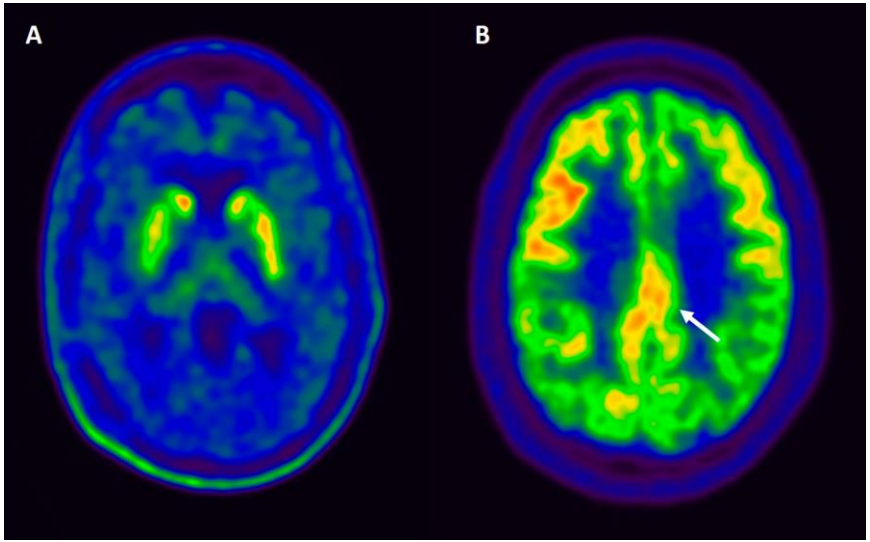
Source: Adapted from McKeith *et al.*[26]

MCI-LB, mild cognitive impairment with Lewy bodies; MIBG, metaiodobenzylguanidine; PET, positron emission tomography; REM, rapid eye movement; SPECT, single-photon emission computed tomography.

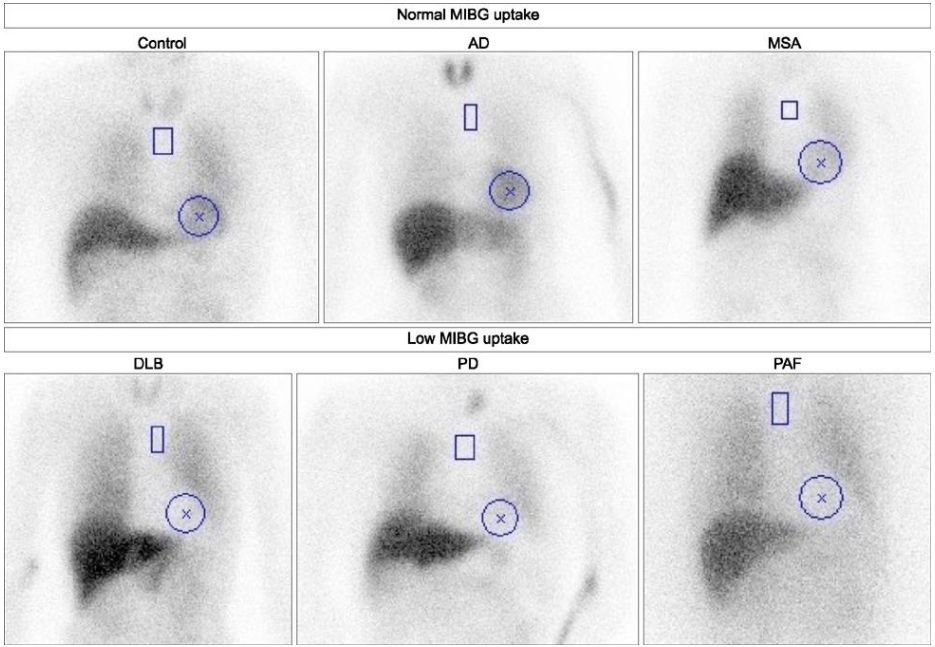
The criteria also include supportive clinical features and potential biomarkers that may be helpful in diagnosing MCI-LB but are not formally part of the criteria (see text).

A. ~10% of individuals met pathological criteria for Lewy body disease while having normal DAT imaging

B. The cingulate island sign (white arrow) on FDG-PET, highly suggestive of DLB



over half of individuals with probable DLB have elevated amyloid deposition on PET scans



α-synuclein real-time quaking-induced conversion (RT-QuIC) assay using CSF & phosphorylated α-synuclein immunofluorescence assay using skin biopsy, now available through some commercial laboratories;
yet to be established in routine clinical diagnosis

Behav. Sci. 2021, 11(7), 94

Progression

Some individuals with DLB never develop parkinsonism in life and those with parkinsonism might or might not have sufficient features for a PD diagnosis.

DLB *versus* AD dementia, mean survival of individuals with DLB was 4.11 ± 4.10 years; individuals with AD dementia (5.66 ± 5.32 years)

Rapid and slowly progressive DLB forms, over 10% of individuals died less than 1 year, while another 10% lived more than 7 years, a small percent lived more than 10 years after diagnosis

Failure to thrive is the most commonly reported cause of death (65%), followed by swallowing difficulties associated with aspiration and pneumonia (23%; multiple causes of death allowed by study).

Management

Treatment for DLB: modest evidence, relies on studies in PD/AD, expert consensus

Behavioral/neuropsychiatric symptoms in DLB: psychosis (visual hallucinations, hallucinations in other modalities, systematized delusions), depression, anxiety, apathy, and aggression

Pharmacological therapy for psychosis is recommended only if symptoms are severe or distressing, and if triggers (e.g. infection) are excluded.

Parkinsonism in DLB is generally treated with levodopa monotherapy. Zonisamide, approved for the treatment of parkinsonism in Japan (MAO-B inhibition)

Table 3. Pharmacological therapies for dementia with Lewy bodies[a].

Symptom	Pharmacological options
Cognitive impairment	Cholinesterase inhibitors (best evidence for donepezil, rivastigmine) Memantine (evidence mixed)
Neuropsychiatric symptoms	Psychosis: Quetiapine, pimavanserin, clozapine Other neuropsychiatric symptoms: SSRIs, SNRIs, memantine
Parkinsonism	Levodopa preparations (e.g. carbidopa/levodopa) Zonisamide (adjunctive)
Autonomic dysfunction	Orthostatic hypotension: midodrine, fludrocortisone, droxidopa Constipation: Stool softeners, laxatives Sialorrhea: Botulinum toxin injections, glycopyrrolate Urinary dysfunction: Mirabegron
REM sleep behavior disorder	Melatonin, clonazepam; potentially memantine

DLB, dementia with Lewy bodies; REM, rapid eye movement; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.
[a]Nonpharmacological therapies and research-only approaches not included. Therapies may be 'off label' for use depending on location and local regulatory determinations. Level of evidence for use of each agent varies in DLB and some of these are pragmatic approaches rather than evidence-based. Treatment should be individualized.

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Parkinson disease Dementia (PDD)

Commonly experienced non-motor symptoms of PD

Domain	Symptom	
Autonomic	• Dribbling • Dysphagia • Nausea • Constipation • Urinary frequency • Urinary urgency	• Nocturia • Sexual dysfunction • Orthostatic hypotension • Supine (recumbent) hypertension • Excessive sweating
Sleep	• Excessive daytime sleepiness • Vivid dreams/REM sleep behaviour disorder	• Insomnia • Restless legs syndrome
Neuropsychiatric	• Cognitive impairment • Mood disorders (depression, anxiety) • Apathy	• Psychosis (hallucinations, delusions) • Impulsive–compulsive behaviours
Sensory and other	• Olfactory, visual, and auditory dysfunction	• Pain • Fatigue

Adapted from: Erro et al. J Parkinson Restless Leg Synd 2015;5:1–10; Schapira et al. Nat Rev Neurosci 2017;18(7):435–450

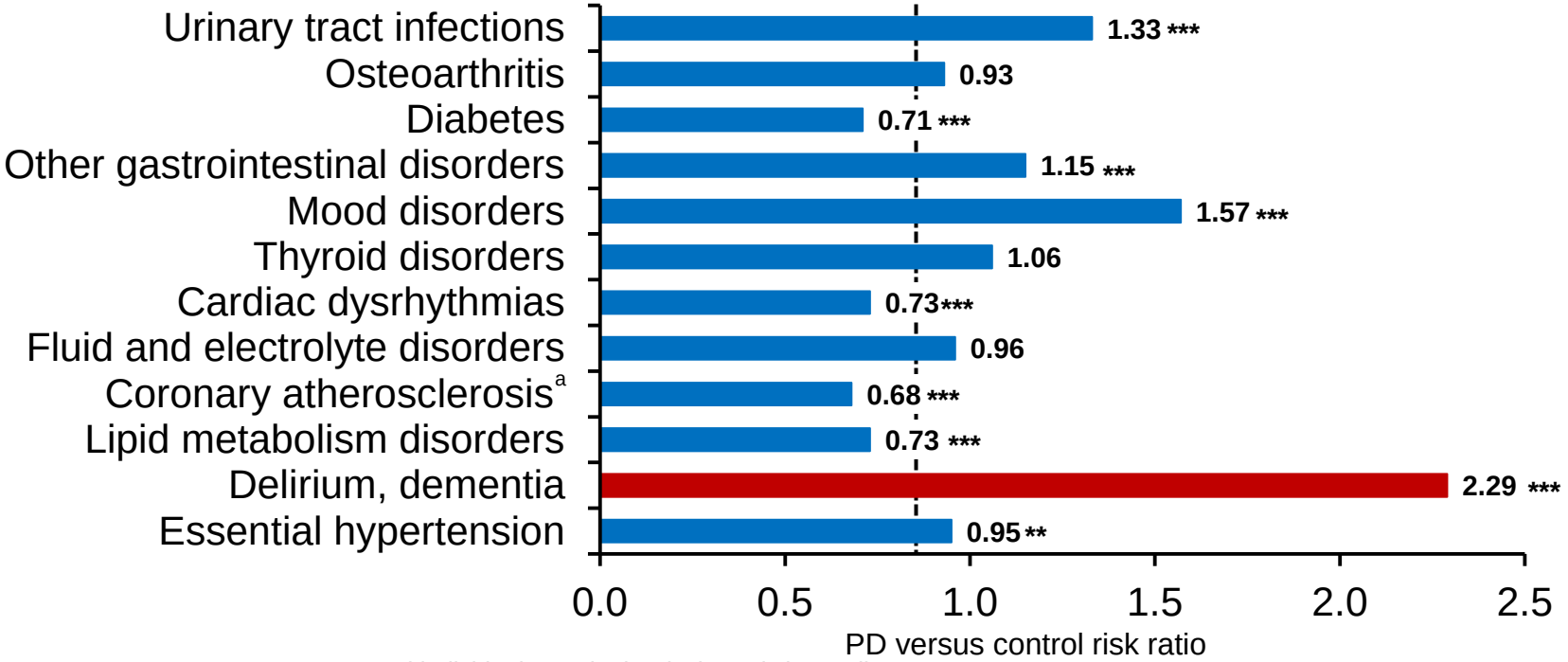
Cognition and cognitive impairment in PD

- A spectrum of cognitive dysfunction, ranging from MCI to PD dementia[1-3]
- MCI in 19% ~ 53% of PD, with most reports in the 20%-30% range.
- Based on a study examined a total of 1,346 patients with PD without dementia, from eight different cohorts, 25.8% of patients with PD were classified as having MCI[4]
- In PD, MCI single domain more common than multiple domain
- MCI in PD affects a range of cognitive domains, including memory, visual–spatial, and attention/executive abilities[4]
- Executive/attention function, and to lesser extent, CVLT immediate recall impairments are associated with development of dementia
- Presence of MCI is associated with increasing age, disease duration, and disease severity[1]

1. Litvan et al. Mov Disord 2012;27(3):349–356; 2. Emre et al. Mov Disord 2007;22(12):1689–1707; 3. Weil et al. Curr Neurol Neurosci Rep 2018;18(4):17; 4. Aarsland et al. Neurology 2010;75(12):1062–1069

Comorbidities of PD

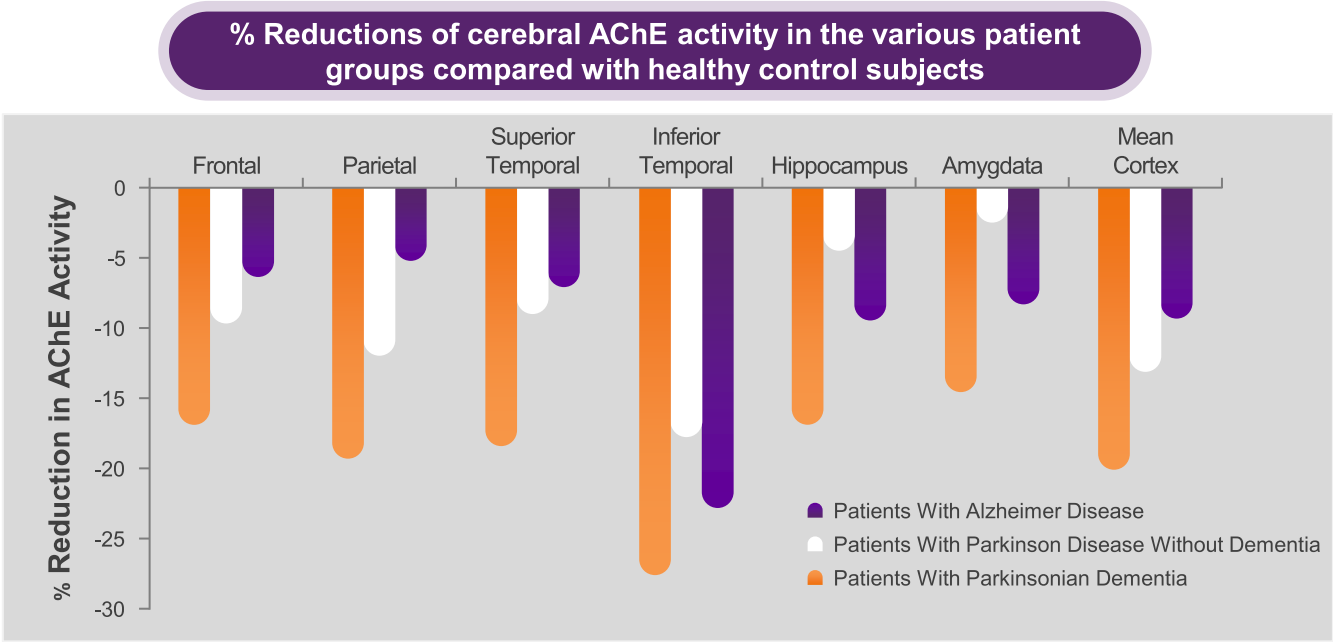
Comparison with control individuals of the 12 most commonly diagnosed comorbid conditions in patients with PD admitted to hospital



**p<0.01, ***p<0.001 versus control individuals [a]and other ischaemic heart disease

Xu et al. Neuroepidemiology 2018;50(1–2):7–17

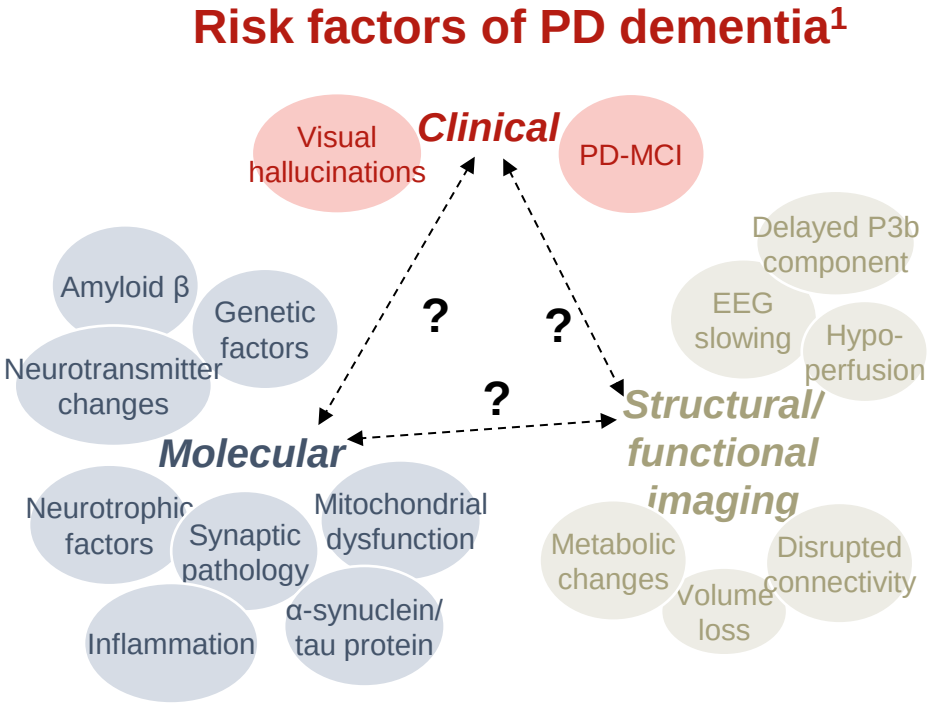
Marked cholinergic deficits in PD



Group comparison design of patients with AD (n=12), PD with dementia (n=14), and Parkinson disease without dementia (n=11), and controls (n=10) who underwent AChE imaging. Patients with AD and PD with dementia had approximately equal dementia severity. Main outcome measures are Cerebral AChE activity measured by cortical [^{11}C] PMP k3 hydrolysis rate.

Bohnen NI, et al. *Arch Neurol*. 2003;60(12):1745-1748.

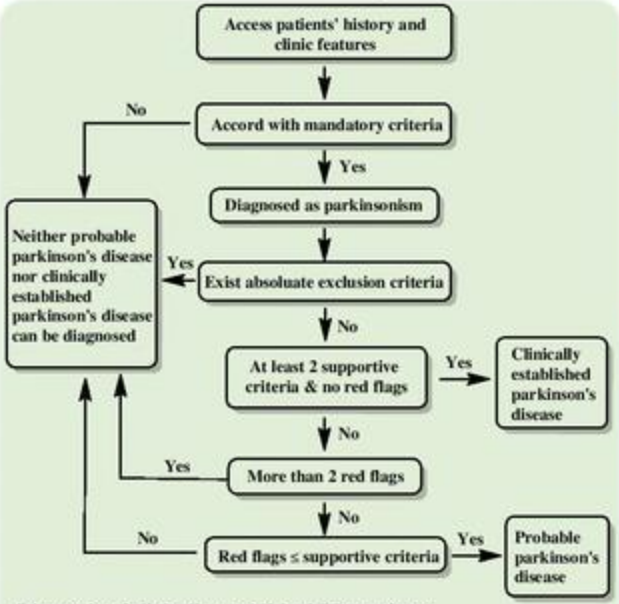
Risk factors of PD dementia



- Most people with Parkinson's develop dementia as a progression of their PD, rather than having both Parkinson's and Alzheimer's.
- Risk factors of PDD
  - Man, Family history of dementia
  - Increasing age, Older age at onset of PD, Longer duration of disease (advanced stage)
  - Severe motor symptoms, Having visual hallucinations

1. Aarsland et al. Nat Rev Neurol 2017;13(4):217–231; 2. Seppi et al. Mov Disord 2019;34(2):180–198

Parkinson's Disease Diagnosis Workflow



Diagnosis of clinically established PD requires:

- 1. Absence of absolute exclusion criteria
- 2. At least two supportive criteria
- 3. No red flags

Diagnosis of clinically probable PD can be made in:

- 1. No absolute exclusion criteria
- 2. Red flags can be counterbalanced by supportive criteria: if 1 red flag is present, there must be counterbalanced at least 1 supportive criterion; if 2 red flags, at least 2 supportive criteria; if red flags > 2, clinically probable PD cannot be diagnosed.

Diagnostic Criteria for Parkinson's Disease

Mandatory criteria

- Bradykinesia plus at least one of rest tremor and/or rigidity

Supportive criteria

1. Clear and dramatic beneficial response to dopaminergic therapy
2. Rest tremor of a limb
3. Presence of levodopa-induced dyskinesia
4. The presence of either olfactory loss or cardiac sympathetic denervation on metaiodobenzylguanidine (MIBG) scintigraphy

Absolute Exclusion criteria

1. Unequivocal cerebellar abnormalities or cerebellar oculomotor abnormalities
2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia within the first 5 years of disease
4. Parkinsonian features restricted to the lower limbs for more than 3 years
5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis), clear limb ideomotor apraxia, or progressive aphasia
8. Normal functional neuroimaging of the presynaptic dopaminergic system
9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than PD

Red flags

1. Rapid progression of gait impairment within 5 years of onset
2. A complete absence of progression of motor symptoms or signs over 5 or more years
3. Early bulbar dysfunction: severe dysphonia or dysarthria or severe dysphagia within the first 5 years
4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
5. Severe autonomic failure in the first 5 years of disease
6. Recurrent (> 1/years) falls because of impaired balance within 3 years of onset
7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 years
8. Absence of any of the common nonmotor features of disease despite 5 years disease duration
9. Otherwise-unexplained pyramidal tract signs
10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance based on objective examination

MDS diagnostic criteria for MCI in PD

I. Inclusion criteria[1]

- **Diagnosis of PD** based on the UK PD Brain Bank Criteria
- Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician
- **Cognitive deficits** on either formal neuropsychological testing or a scale of global cognitive abilities (detailed in Section III)
- Cognitive deficits not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present

II. Exclusion criteria[1]

- **Diagnosis of PD dementia** based on MDS Task Force proposed criteria[2]
- **Other primary explanations for cognitive impairment** (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma)
- **Other PD-associated comorbid conditions** (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing

III. Specific guidelines for PD–MCI Level I and Level II categories[1]

A. Level I (abbreviated assessment)

- **Impairment on a scale of global cognitive abilities** validated for use in PD

or

- **Impairment on at least two tests**, when a limited battery of neuropsychological tests is performed (i.e., the battery includes less than two tests within each of the five cognitive domains or less than five cognitive domains are assessed)

B. Level II (comprehensive assessment)

- Neuropsychological testing that includes two tests within each of the five cognitive domains (i.e., attention and working memory, executive, language, memory, and visuospatial)
- **Impairment on at least two neuropsychological tests**, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains
- Impairment on neuropsychological tests may be demonstrated by:
  - Performance approximately **1 to 2 standard deviations below appropriate norms**
  - **Significant decline** demonstrated on serial cognitive testing
  - **Significant decline** from estimated premorbid levels

1. Litvan et al. Mov Disord 2012;27(3):349–356; 2. Emre et al. Mov Disord 2007;22(12):1689–1707

Diagnostic criteria for dementia in PD

MDS-proposed criteria for dementia in PD[1-3]

1. **Core features:** **Diagnosis of PD & dementia** syndrome
2. **Associated clinical features:** Impairment of **at least 2** of 4 cognitive domains (may be supported by behavioural symptoms)

Features which make diagnosis uncertain

- Coexistence of any abnormality that could itself cause cognitive impairment, but not cause dementia
- Unknown time interval between onset of motor and cognitive symptoms

Features which make diagnosis impossible

Cognitive and behavioural symptoms presenting as a result of other conditions, for example:

- Acute confusion due to systemic diseases/abnormalities or drug intoxication
- Major depression according to DSM-IV
- Features of 'probable vascular dementia' according to NINDS–AIREN

- The risk of developing dementia for patients with PD, at any time, is approximately 4–6 times that for people of a similar age without PD[2]
- Dementia also seems to be more prevalent in patients with motor symptoms dominated by postural instability–gait difficulty symptoms, rather than in those for whom tremor is dominant[2]
- The criteria particularly focus on the timing of dementia symptoms; they should follow the onset of motor symptoms by ≥1 year[3]
- This distinguishes PD-related dementia from dementia with Lewy bodies (DLB)[1]

1. Poewe et al. Int J Clin Pract 2008;62(10):1581–1587; 2. Emre et al. Mov Disord 2007;22(12):1689–1707; 3. Dubois et al. Mov Disord 2007;22(16):2314–2324

Management of cognitive symptoms in PD

Pharmacological therapies

There is some good evidence to support the use of AchE-inhibitors, and some other antidementia drugs[1,2]

Non-pharmacological therapies

Cognitive training routines have been investigated to improve cognition in PD[1]

Some evidence suggests that *physical exercise* can improve non-motor symptoms, including cognition in patients with PD[1]

Some studies have suggested *deep brain stimulation* could be effective in patients with PD and cognitive symptoms[1]

1. Aarsland et al. Nat Rev Neurol 2017;13(4):217–231; 2. Seppi et al. Mov Disord 2019;34(2):180–198

Clinically available pharmacologic treatments for Cognition in PD-MCI and PDD

Category	Specific Agents	MCI	Dementia	Most Common AEs	Severe but Rare AEs
Cholinesterase inhibitors	Rivastigmine	**Investigational** [3]	**Clinically useful** [1]	Capsules: Nausea, Vomiting, weight loss Patch: nausea, vomiting, falls	Capsules: atrial fibrillation, myocardial infarction, hypokalemia, transient ischemic attack, seizures. Patch: dehydration
	Donepezil	Not studied	**Possibly useful** [2]	Nausea, diarrhea, vomiting	Gastrointestinal hemorrhage, heart block, torsades de pointes
	Galantamine	Not studied	**Possibly useful** [2]	Nausea, vomiting, diarrhea	Syncope, Stevens–Johnson syndrome, gastrointestinal hemorrhage, seizure
NMDA Receptor Antagonist	Memantine	Not studied	**Investigational** [3]	Diarrhea, constipation, confusion, dizziness	Stroke, seizure, renal failure
Dopaminergic therapy	Rasagiline (monoamine oxidase B inhibitor)	**Investigational** [3]	Not studied	Orthostatic hypotension, headache, nausea	Serotonin syndrome
Selective norepinephrine reuptake inhibitor	Atomoxetine	**Investigational**	Not studied	Increased heart rate, nausea, decreased appetite, xerostomia	Sudden cardiac death, stroke

Clinically useful (1), Possibly useful (2), and Investigational (3) as determined by the International Parkinson and MDS Evidence-Based Medicine Review. Behav. Sci. 2021, 11(4), 54

CHA 의과학대학교
CHA 분당차병원

Thank you for listening

기억력센터