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

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Introduction

The umbrella term Lewy body dementia include:

- Parkinson’s disease dementia (PDD)
- Dementia with Lewy bodies (DLB)

Case 1

A 75-year-old patient, a retired engineer, was admitted to the memory clinic for progressive memory loss for 1 year and behavior change for 1 month.

In the last five years, the patient experienced hypoactive, and Parkinson’s disease was diagnosed based on the persistence of extrapyramidal symptoms and he was well responding to a combination of levodopa and carbidopa.

On examination showed moderate bradykinesia (R>L), mild rigidity and postural instability. His MMSE was 17/30. Others neurological examinations are normal.

Introduction

- Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are different clinical syndromes that share the same pathological hallmark, namely Lewy body disease, in which post-mortem examination shows neuronal α-synuclein inclusions (Lewy bodies) and neuronal loss.
- Both variants typically cause both movement problems and cognitive symptoms.
- The distinction, and therefore which diagnosis a person receives, depends on the order in which symptoms are observed and how closely together.
- Over time, people with DLB and PDD tend to develop similar symptoms.

Risk Factors for Parkinson's Disease Dementia

- Older age
- Greater severity of motor symptoms
- Having mild cognitive impairment
- Visual hallucinations (with no other dementia symptoms)
- Excessive daytime sleepiness
- Depression
- Family history of dementia
- Freezing of gait
- Longer duration of Parkinson's disease in the advanced stage
- Being male

Case 1 (Continued)

- In addition, neurocognitive function assessment showed impairment in cognitive domains (including attention, executive functions, visuo-spatial functions, memory and language).

Criteria for the Diagnosis of Probable Parkinson's Disease Dementia

A. Core features must be both present.

1. **Diagnosis of Parkinson's disease** according to specific "diagnostic criteria"

2. A **syndrome of "cognitive decline"** with insidious onset and slow progression, developing within the context of established PD and diagnosed by history, clinical, and mental examination, defined as:

- Impairment in more than one cognitive domain (including: attention, executive functions, visuo-spatial functions, memory and language).
- Decline from a premorbid level of functioning.
- Deficits severe enough to impair daily life (social, occupational, or personal care), regardless of the impairment from motor or autonomic symptoms.

Criteria for the Diagnosis of Probable Parkinson's Disease Dementia (Cont:)

B. Associated clinical features.

- Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall which usually improves with cueing).
- Behavioral features such as apathy, changes in personality and mood, hallucinations, delusions, and excessive daytime sleepiness may be present (but are not necessary for diagnosis).

Criteria for the Diagnosis of Probable Parkinson's Disease Dementia (Cont:)

C. Features which do not exclude PDD, but make the diagnosis uncertain

- Existence of any other abnormality which may cause cognitive impairment but is not as the cause of dementia, e.g., presence of relevant vascular disease in imaging.
- The time interval between the development of motor and cognitive symptoms is unknown

D. There are none of the following features suggesting other conditions or diseases as the cause of mental impairment, which would hinder an accurate diagnosis of PDD: delirium, diagnosis of major depression, evidence for diagnosis of probable vascular dementia.

Criteria for the Diagnosis of Possible Parkinson's Disease Dementia

A. Core features must be both present.

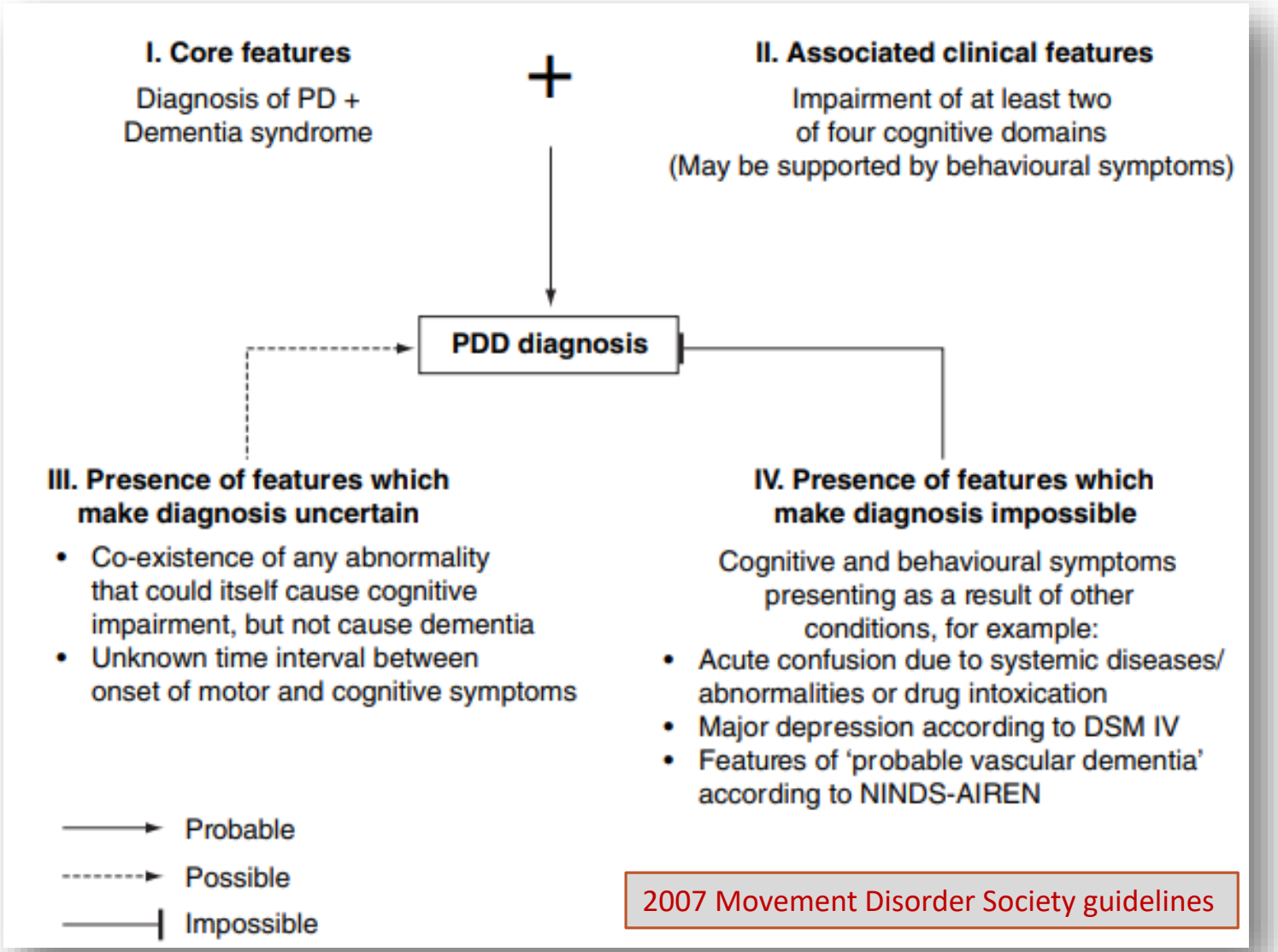
B. The cognitive decline presents with atypical profile of cognitive impairment in one or more domains, such as prominent or receptive (fluent) aphasia or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention. **or**

C. There are features that make the diagnosis uncertain (e.g., presence of relevant vascular disease in imaging). **or**

D. Time interval between the development of motor and cognitive symptoms is unknown ("1-year rule") **or**

E. There are features suggesting other conditions or diseases as causes of mental impairment (delirium, diagnosis of major depression, evidence for diagnosis of probable vascular dementia)

Parkinson's Disease Dementia (PDD) Diagnosis



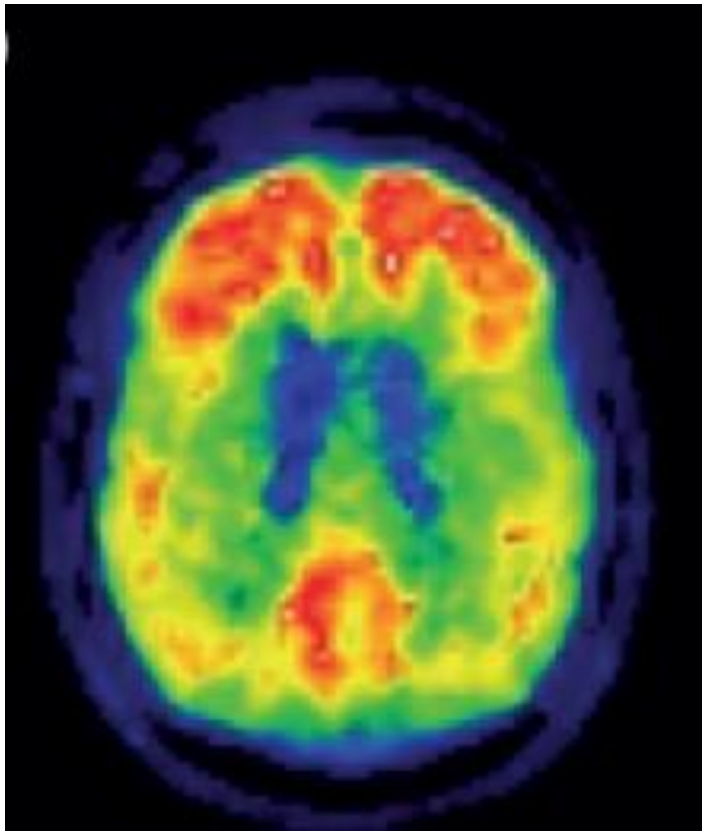
A Simple Algorithm for Clinician Diagnosis of PDD, as Recommended by the MDS Task Force

	Criteria	Assessment
1	A diagnosis of PD	Queen's Square Brain Bank Criteria
2	PD developed prior to the onset of dementia	Patient/caregiver history or ancillary records
3	PD associated with a decreased global cognitive efficiency	MMSE < 26
4	Cognitive deficiency severe enough to impair daily life	Caregiver interview or pill questionnaire
5	Impairment of more than one cognitive domain	Impairment of at least two of the following domains Attention Executive function Visuo-constructive ability Memory

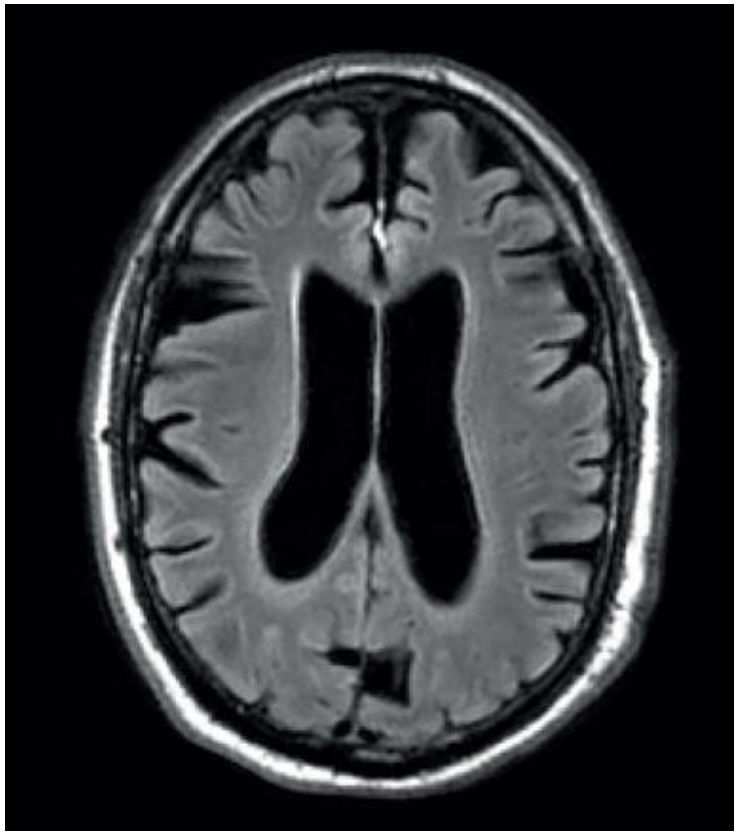
Tests Proposed by the MDS Task Force to Assess Cognitive Deficits in the Clinical Setting

Cognitive domain	Proposed tests	Cut-off scores
Attention	Serial 7s of the MMSE Repeatedly subtract 7 starting at 100	Two or more incorrect responses
	Months reversed Give months of the year backwards	Omission of two or more months
Executive function	Lexical fluency e.g. list words beginning with S in 1 min	Less than 9 words in a minute
	Clock-drawing test Draw clock with hands at '10 past 2'	Inability to draw clock or show time
Visuo-constructive ability	MMSE pentagons Copy two overlapping pentagons	Inability to draw pentagons
Memory	3-word recall of the MMSE Free recall of three words	Missing at least one word

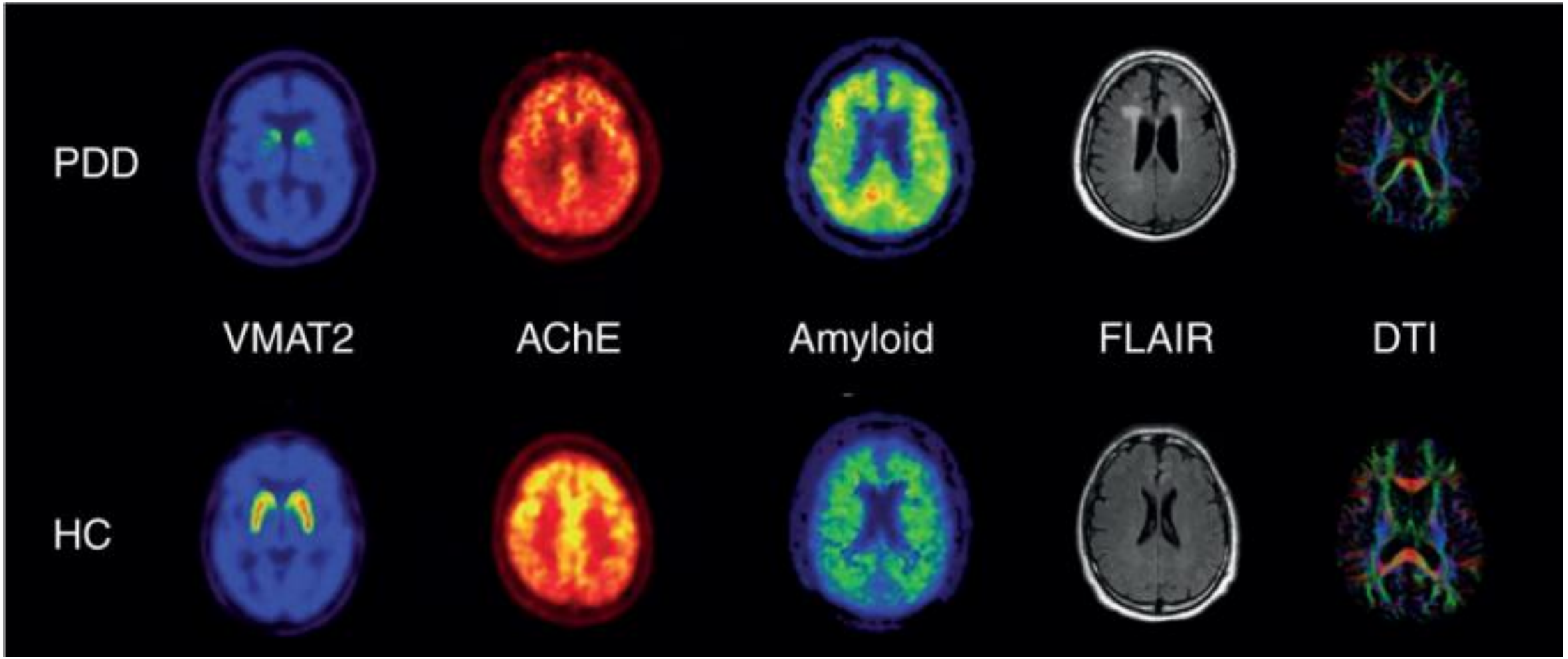
Case 1 (Continued)



11C-Pittsburgh Compound B PET Images- Abnormal elevated binding (seen in Parkinson's disease with dementia)



MRI - global atrophy and enlarged ventricles (seen in Parkinson's disease with dementia)



The multitracer PET studies show significant nigrostriatal dopaminergic losses (VMAT2- PET), cholinergic denervation (AchE-PET), mildly elevated but abnormal amyloid binding (11C-Pittsburgh compound B PET), leukoaraiosis (FLAIR-MRI) and microstructural white matter tract changes (DTI-MRI). The imaging findings illustrate the multifactorial and heterogeneous nature processes of parkinsonian dementia. AchE: Acetylcholinesterase; DTI: Diffusion tensor imaging; FLAIR: Fluid-attenuated inversion recovery; HC: Healthy control; PDD: Parkinson's disease with dementia; VMAT2: Vesicular monoamine transporter 2.

Case 1 (Continued)

This Patient has Core Features with Cognitive Decline and Imaging Features of PDD

Case 2

A 71-year-old patient, a retired sailor, was admitted to the hospital for diagnostic check-up and treatment of organic hallucinosis and extrapyramidal symptoms.

Visual hallucinations appeared every day & he saw a person he knew but it was not real.

It resulted in intensified visual hallucinations, and the patient described it as seeing the crew and ships.

At the same time, the patient experienced deterioration of daily functioning with a marked decline in decision making.

Shortly before hospitalization, the patient was examined at a psychiatric outpatient clinic and was diagnosed with organic hallucinosis and a depressive episode.

Escitalopram and olanzapine were introduced in therapy, but the patient did not adhere to treatment recommendations.

Case 2 (Continued)

During the examination, he complained of frequent urination and constipation.

He denied taking any psychoactive substances.

On the day of hospital admission, the patient was occasionally disoriented, he responded with short latency, along with psychomotor slowing.

Also, cogwheeling effect and lead-pipe resistance were mildly indicated.

His thought flow was mildly slowed without any delusions in the thought content.

Case 2 (Continued)

He confirmed complex visual hallucinations which he described in detail with affective engagement.

In the domain of personality, he seemed inclined to suppression and projection with occasionally reduced tolerance to external frustration.

The patient’s cognitive functions fluctuated throughout the day, primarily with impairment of executive functions.

Neurological testing revealed dysarthria, bradykinesia, and elevated muscle tone of extrapyramidal type in all extremities, without loss of sensation.

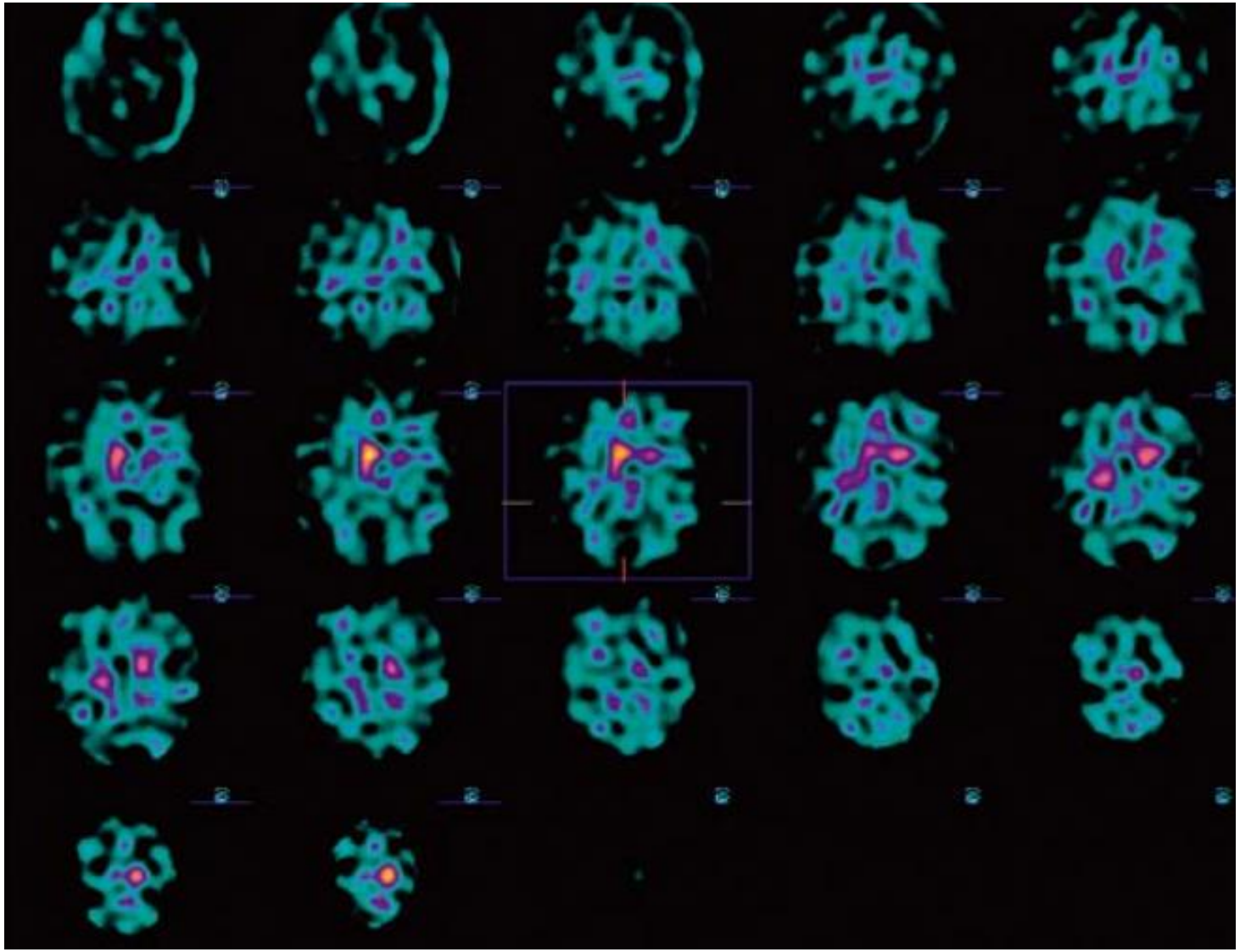
In Romberg’s position, there was latero- and retropulsion, while walking was characterized by smaller steps.

Case 2 (Continued)

Routine laboratory check-up revealed no significant deviations.

Brain MRI showed diffuse atrophic changes of the brain with widening of the subarachnoid fluid space and brain sulci in frontoparietal and temporo-occipital region and atrophic changes of the cerebellum with expanded peri-cerebellar fluid spaces.

Basal brain activity was elevated along with severe functional impairment of the striatal dopamine system.



Case 2 (Continued)

SPECT scan with 123-I Ioflupane showing Elevated Basal Brain Activity, along with Severe Functional Impairment of the Striatal Dopamine System.

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

Core clinical features (*The first 3 typically occur early and may persist throughout the course.*)

Fluctuating cognition with pronounced variations in attention and alertness.
Recurrent visual hallucinations that are typically well formed and detailed.
REM sleep behavior disorder, *which may precede cognitive decline.*
One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Supportive clinical features

Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

Indicative biomarkers

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

Supportive biomarkers

Relative preservation of medial temporal lobe structures on CT/MRI scan.
Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging.
Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

Revised criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)

Table 2. The Lewy body composite risk score

Lewy body composite risk score		
Please rate the following physical findings as being present or absent for the past six months and symptoms as being present or absent for at least three times over the past six months. Does the patient:	***YES***	***NO***
1. Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?		
2. Have rigidity (with or without cogwheeling) on passive range of motion in any of the limbs?		
3. Have a loss of postural stability with or without frequent falls?		
4. Have tremor at rest in any of the limbs or the head?		
5. Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?		
6. Have episodes of illogical thinking or incoherent, random thoughts?		
7. Have frequent staring spells or periods of blank looks?		
8. Have visual hallucinations?		
9. Appear to act out their dreams?		
10. Have orthostatic hypotension or other signs of autonomic insufficiency?		
Total score: __/10		

Adapted from 'Improving the clinical detection of Lewy body dementia with the Lewy body composite risk score'.[15]

The LBCRS is scored on a scale from 0 to 10. A score of 0–2 indicates non-DLB cases, with a score of 3–10 indicating probable DLB.

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Case 2 (Continued)

Considering the diagnostic workup performed (clinical signs and neuroradiological confirmation), the diagnosis of DLB was made and pharmacotherapy was revised.

During hospitalization, pramipexole was excluded from therapy due to worsening of visual hallucinations, while levodopa/carbidopa was continued at a dose of 250/25 mg TID.

Rivastigmine was also introduced at a dose of 3 mg daily and divided into morning and evening applications as an acetylcholinesterase inhibitor recommended for the treatment of this type of dementia.

Due to complex hallucinatory experiences and consequential affective engagement, clozapine was administered as an evening dose of 25 mg.

Visual hallucinations then diminished and ceased, while the extrapyramidal symptoms were less pronounced, as well as cognitive fluctuations, with absence of delirium episodes and normalization of circadian rhythm.

Criteria for the Diagnosis of Probable and Possible Dementia with Lewy Bodies

Diagnosis is **probable** when:

- Two or more core clinical features are present

OR

- Only one core clinical feature is present but with one or more indicative biomarkers

Probable DLB **should not be diagnosed** based on biomarkers alone.

Diagnosis is **possible** when:

- Only one core clinical feature (with no biomarkers)
- One or more indicative biomarkers are present without core clinical features.

Criteria for the Diagnosis of Probable and Possible Dementia with Lewy Bodies (Cont:)

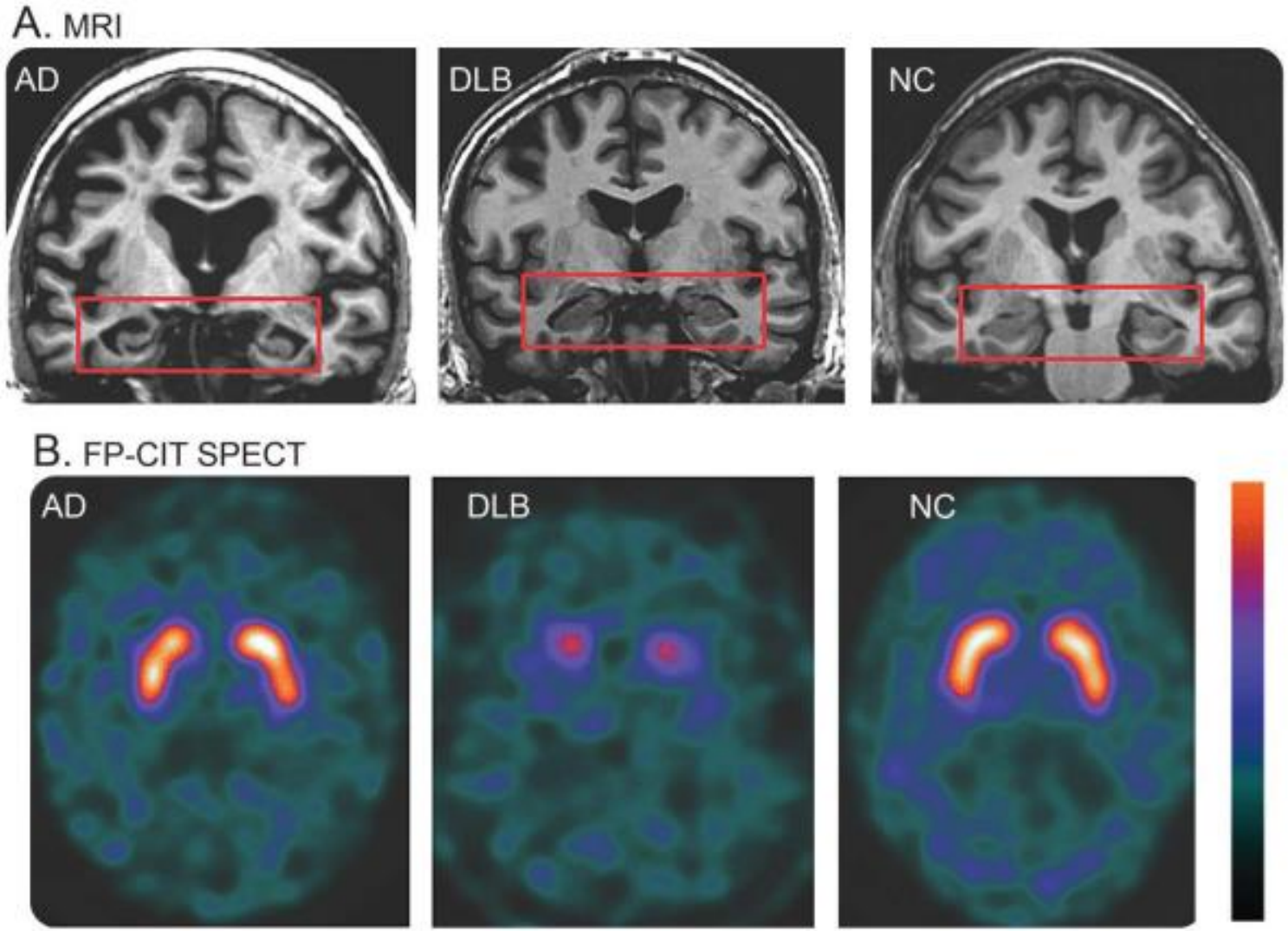
DLB is less likely:

A. In the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation, or

B. If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia.

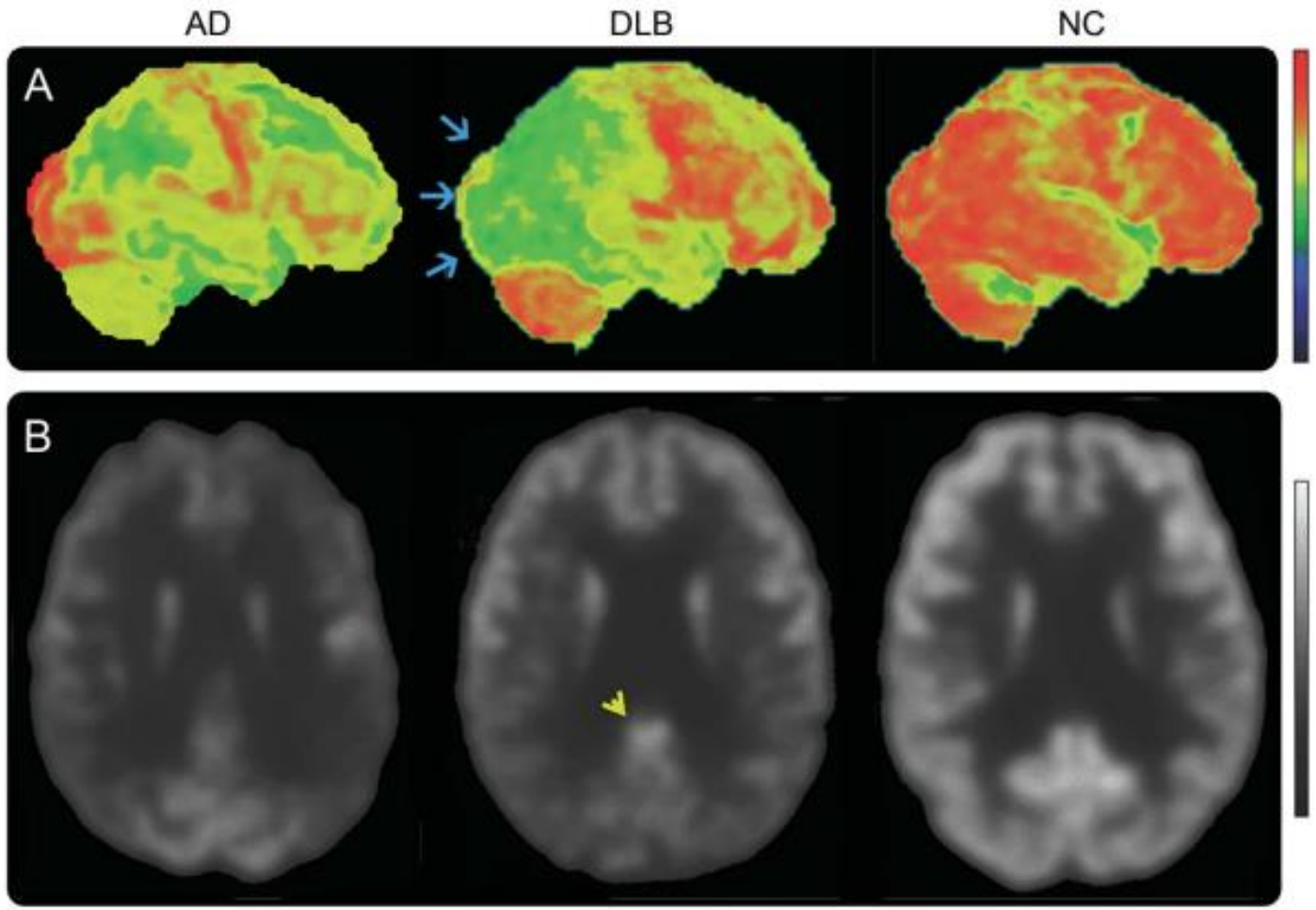
DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism.

Coronal T1-weighted MRI and 123iodine FP-CIT SPECT images in Alzheimer disease (AD), dementia with Lewy bodies (DLB), and normal controls (NC)



(A) On the MRI, note the relative preservation of medial temporal lobe volume (rectangles) in DLB, which is similar to NC, whereas atrophy is obvious in AD. (B) On the FP-CIT SPECT images, note the minimal uptake in DLB, which is restricted to the caudate (period or full-stop appearance) compared to the robust uptake in the caudate and putamen in AD and NC (comma appearance).

18F-FDG-PET images in Alzheimer disease (AD), dementia with Lewy bodies (DLB), and normal controls (NC)

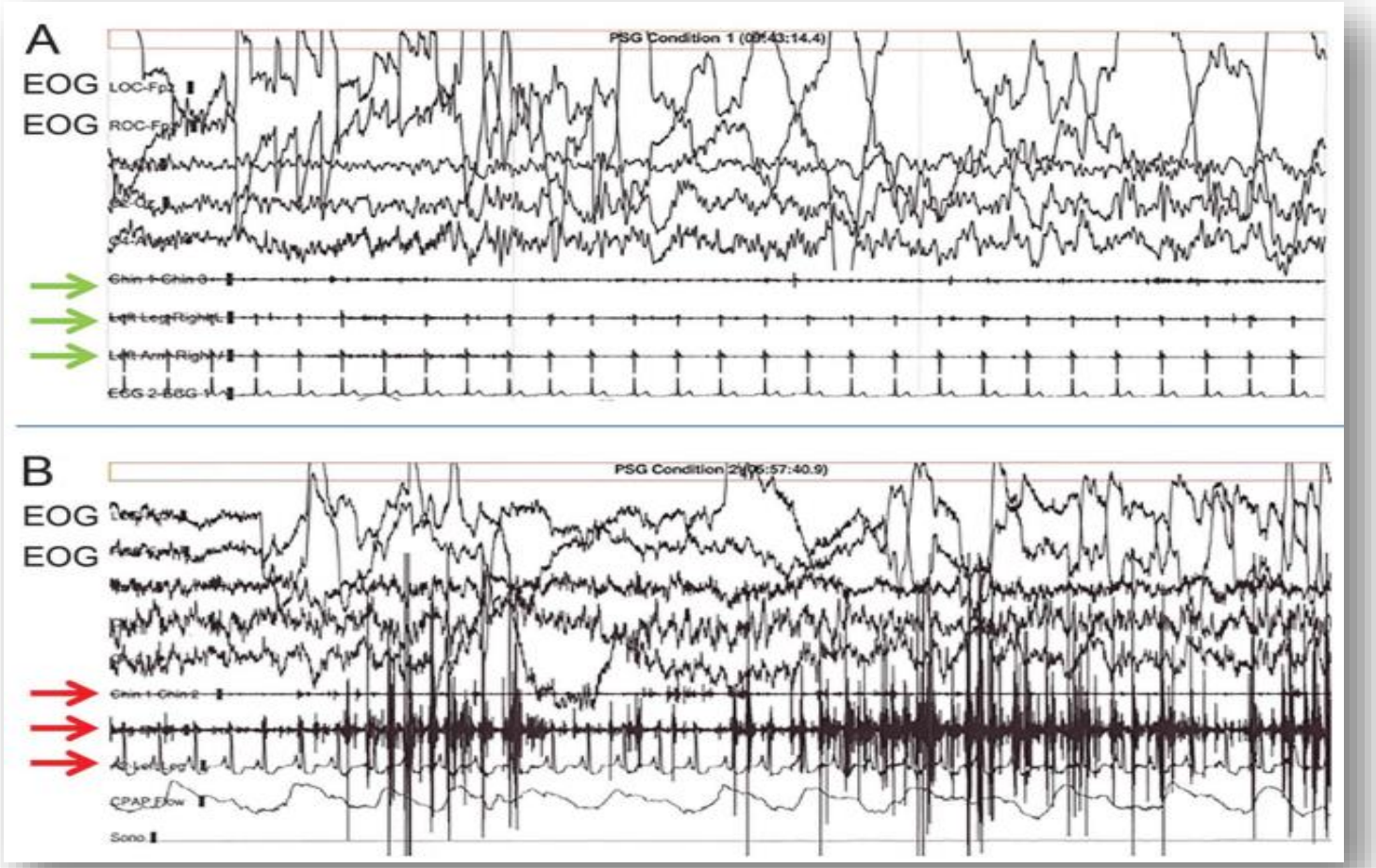


(A) Right lateral metabolic surface map projection.
(B) Standard axial view transecting the posterior cingulate region. Occipital lobe metabolism is preserved in AD and NC but reduced (blue arrows) in DLB. Hypometabolism in AD is predominantly in the temporal, parietal, and frontal regions. There is normal metabolism as reflected by the normal 18F-FDG uptake (lighter shade of gray) in the posterior cingulate region (yellow arrowhead) surrounded by reduced 18F-FDG uptake (darker gray) in the adjacent occipital cortex in DLB, representing the cingulate island sign. This contrasts with the relatively reduced 18F-FDG uptake in the posterior cingulate and relatively preserved 18F-FDG uptake in the occipital cortex regions in AD. In the control, there is normal 18F-FDG uptake in the posterior cingulate, occipital, and other neocortical regions. Color and grayscale sidebars show increasing degrees of deviation from normal as the signal trends lower in the sidebars (red is normal while black is maximally abnormal in color images; white is normal while black is maximally abnormal in grayscale images).

Glucose metabolic differences between Parkinson's disease without dementia, Parkinson's disease with dementia/dementia with Lewy bodies and Alzheimer's disease.

Brain region	PD without dementia	PDD/DLB	Alzheimer's disease
Striatum	Preserved to ↑	↓ (especially caudate nucleus)	Preserved
Thalamus	Preserved	↓	Preserved
Parietotemporal cortices	Preserved	↓	↓↓
Posterior cingulate cortex	Preserved	↓↓	↓↓
Frontal cortex	Preserved	Variable ↓	Variable ↓
Occipital cortex	Brodmann area 17 ↓	Brodmann areas 17, 18 and 19 ↓↓	Preserved

Polysomnographic (PSG) Recordings



PSG recordings of normal REM sleep (A) and REM sleep without atonia, typical of REM sleep behavior disorder (B).REM are reflected by the high-amplitude, abrupt deviations from baseline in the electro-oculogram (EOG) leads during a 30-second epoch. In (A), note the absence of EMG activity in the submental, leg, and arm leads (green arrows), whereas increased EMG tone is present in the same leads (red arrows) in B, particularly in the middle (arm lead), in this patient.

Differential Diagnosis of Patients with Dementia with Lewy Bodies (DLB)

OTHER DEMENTIAS

- Alzheimer disease
- Frontotemporal dementias
- Vascular dementia

OTHER NEUROLOGIC ILLNESSES

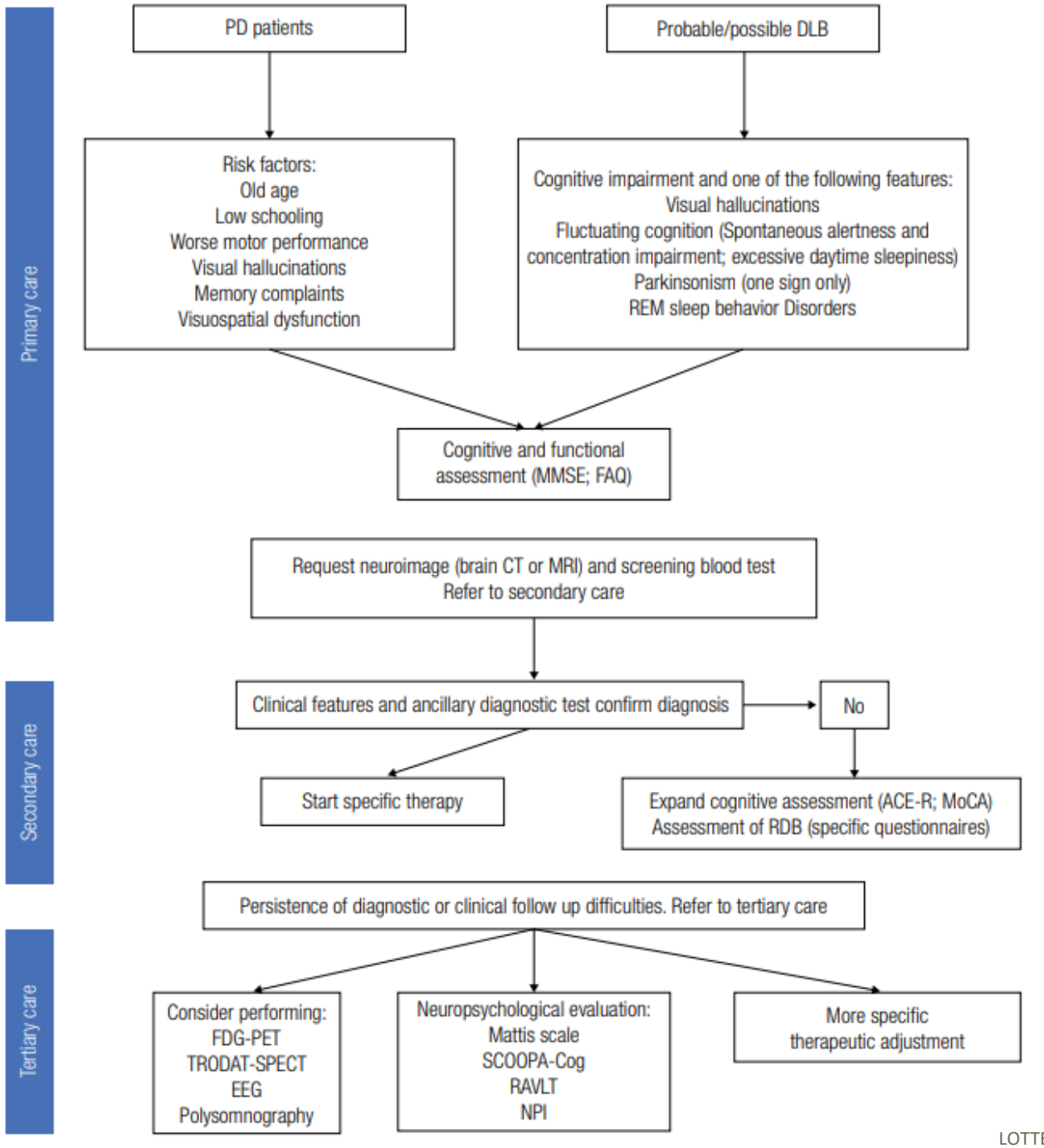
- Idiopathic Parkinson disease
- Multisystem atrophy
- Supranuclear palsy
- Creuzfeldt-Jakob disease

OTHER PSYCHIATRIC ILLNESSES

- Mania
- Psychotic depression
- Late-onset delusional disorder

CAUSES OF DELIRIUM

- Infection Metabolic and endocrine causes
- Medications
- Stroke and vascular causes
- Withdrawal (medication and alcohol)

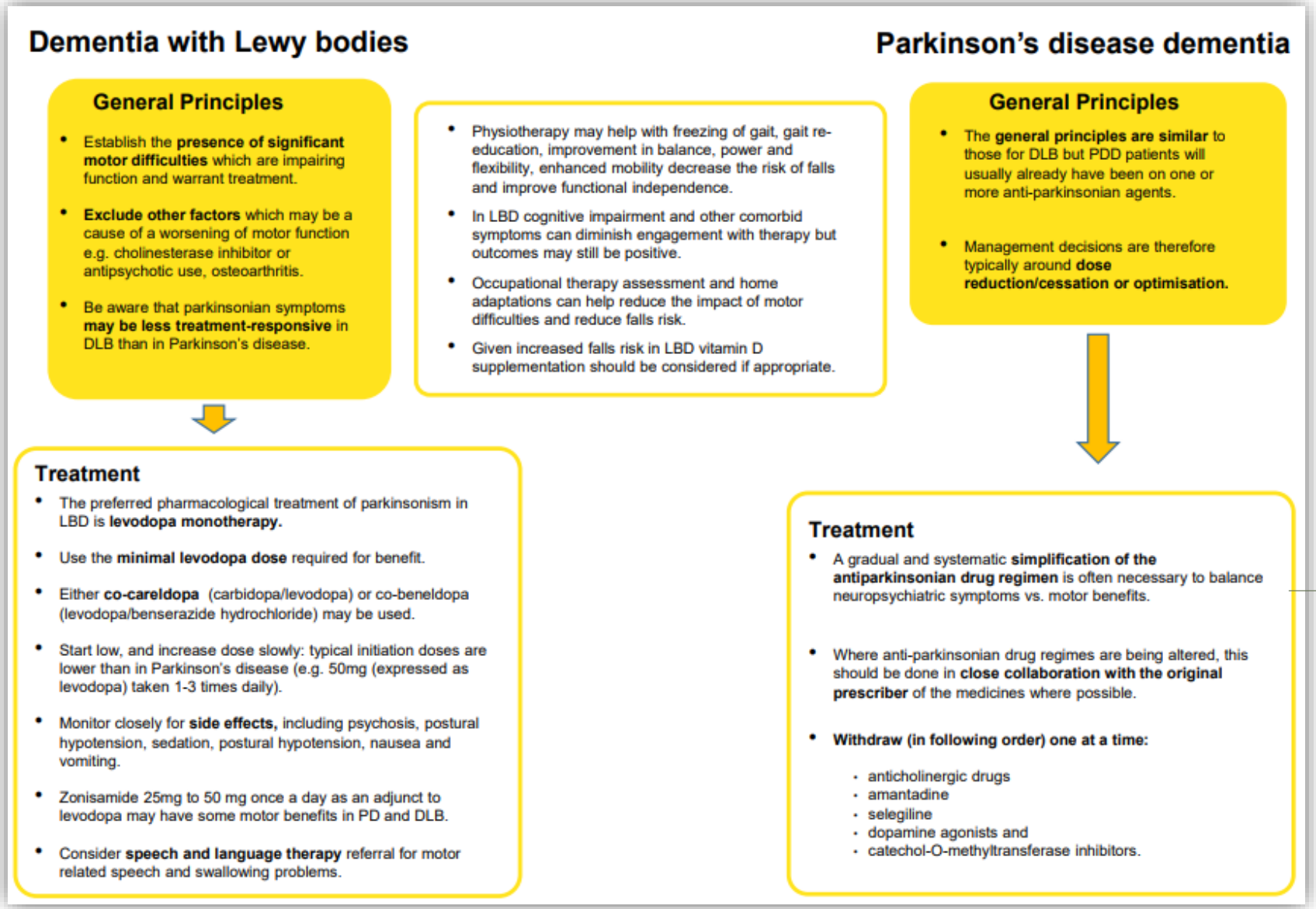


Flowchart of the approach to patients with parkinsonism and dementia

Management of Lewy body dementia

Parkinson's Disease Dementia (PDD)
Dementia with Lewy Bodies (DLB)

Treatment of Motor Symptoms



Neuropsychiatric Symptoms

Neuropsychiatric Symptoms

General Principles

- Establish the **presence, severity and impact** of significant neuropsychiatric symptoms warranting treatment. These may include **visual hallucinations, hallucinations in other modalities, delusions and apathy.**
- Obtain **collateral history** for symptoms from reports of the patient and an informed carer. Systematic **rating scales** may be helpful.
- **Other factors causing or aggravating** mood and behaviour disturbance should be excluded e.g. physical illness, pain or discomfort, environmental precipitants, agitation & aggression, depression & anxiety.

Cholinesterase Inhibitor use

- Consider as a first line treatment.
- Choice will be influenced by previous experience, ease of administration, dose titration regime and side effect profile.
- Donepezil and rivastigmine are similarly effective in DLB.
- There is more evidence for the benefits/effectiveness of rivastigmine in PDD.
- There is less evidence for the use of galantamine in LBD.

- Before starting Cholinesterase Inhibitors (ChEIs)
  - Check for clinically significant cardiovascular disease, particularly orthostatic hypotension, syncope or pre-syncope or cardiac dysrhythmia / conduction disturbance or bradycardia.
  - Consider carrying out an ECG before ChEI, particularly if there is a history of cardiac issues and/or autonomic dysfunction.
  - Cardiology referral should be made in cases of uncertainty including decisions regarding fitting of pacemakers.

- Cholinesterase inhibitors are best **titrated to the maximum tolerated dose** and maintained at this level.
  - **Donepezil**: 5mg once daily for 4-6 weeks, increased to 10mg daily if no significant side effects occur.
  - **Rivastigmine (oral)**: 1.5 mg twice daily for 4 weeks, increased to 3 mg twice daily ideally. Dose can be increased up to 4.5 mg twice daily going up to 6 mg twice daily if no significant side effects occur.
  - **Rivastigmine patch:** Dosing and titration is typically 4.6 mg/24 hours for 4 weeks, increased to 9.5 mg/24 hours with a further increase to 13.3 mg/24hours if no significant side effects. May have advantages in patients with swallowing difficulties, gastrointestinal side-effects in response to oral agents, compliance issues, or if there is a history of significant response variation to oral dosing.
  - **Galantamine:** 8mg/day increased to the initial maintenance dose of 16mg/day after a minimum of 4-6 weeks. A further increase of 24mg/day of galantamine can be attempted after 4 weeks at 16mg/day if no significant side effects occur.

- **Assessing response and deciding about continuation:**
  - Global and behavioural / psychiatric baseline symptoms should be documented.
  - Assess outcome after 3-6 months on maximum tolerated dose (although some patients neuropsychiatric symptom improvement may be judged earlier).Once optimised treatment should be continued for as long as the patient/carer/clinician consensus is that there are positive benefits.
  - If/when discontinued, ChEIs should be withdrawn gradually as there are reports of a rebound worsening of symptoms.
  - Strategies for non-response or poor tolerance to one ChEI include switching to another ChEI.

- **Adverse effects** include gastrointestinal symptoms, postural hypotension, urinary frequency, hyper-salivation, watering eyes, runny nose and worsening of extrapyramidal motor symptoms, particularly fine tremor. Adverse effects may improve with dose reduction.

Antipsychotic use

- There should be a full discussion with the person with dementia and/or carers about the possible benefits and risks of antipsychotic treatment. This should be recorded in medical notes.
- Watch for severe antipsychotic sensitivity reactions.
- **Be aware of the significant mortality and morbidity associated with the use of antipsychotics in dementia and Parkinson's disease.**
- Identify target symptoms and monitor these regularly.
- Watch for worsening of cognition and more subtle deteriorations in motor function.
- The choice of antipsychotic should be made after an individual risk–benefit analysis.
  - Clozapine, which is effective in PD psychosis, may also help in LBD, although the evidence is lacking.
  - There is no evidence to favour any individual anti-psychotic drug in LBD although atypicals and low potency agents such as quetiapine appear to have the least side effects.
- The lowest possible dose should be initiated and then titrated upwards.
- Treatment should be time limited and regularly reviewed.

Specific symptoms

- **Visual hallucinations**
  - Not all visual hallucinations need treating as in some the hallucinations may be regarded neutrally or sometimes even comforting/pleasurable.
  - Simple explanation of visual symptoms as a consequence of impaired visual processing may allay fears and avoid the need for medication.
  - Interventions such as removing cushions, patterned curtains and other stimuli that might precipitate visual misinterpretations can be helpful, as is provision of good lighting.
  - ChEI are a first line pharmacological treatment for visual hallucinations in LBD. If these are ineffective a trial of an antipsychotic agent may need to be considered.
- **Delusions**
  - Delusions of misidentification, jealousy and paranoia can occur.
  - They are often associated with visual hallucinations and may improve with ChEI (first line) and antipsychotics (second line).
- **Apathy**
  - Providing adequate environmental stimulation may help reduce apathy and it may also improve with a ChEI. There is no evidence to support the use of psychostimulants.
- **Depression and Anxiety**
  - Consider use of social interventions to enhance mood.
  - Avoid antidepressants with significant anti-cholinergic side effects such as tricyclics.
  - Evidence for antidepressant drug efficacy and tolerability in LBD is limited. Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors have an evidence base in Parkinson's disease.
  - Whilst there is no evidence base, ChEI may help some particularly if there is an apathy component.
- **Agitation and Aggression**
  - Often multi-factorial in cause: identify the relevant anteceedent and perpetuating factors and treat as appropriate.
  - Sometimes, if driven by hallucinatory and other psychotic symptoms, agitation and aggression may improve when these are treated with a ChEI first line; anti-psychotics second line.
  - There is currently no evidence for efficacy of other medications in treating agitation or aggression in LBD.

Cognitive Symptoms

Cognitive Symptoms

General Principles

- Establish the presence of significant cognitive difficulties warranting treatment. Impairments in cognition can fluctuate and may relate to:
  - **memory**
  - **attention**
  - **executive functioning**
  - **visuoperceptual abilities**
  - **disorganised speech/communication**.
- Evidence of cognitive difficulties should be obtained from reports by the **patient** and an informed **carer,** and from the results of **formal cognitive testing**.
- Cognitive **fluctuations**, whilst intrinsic to LBD, may also be a feature of **delirium**. Therefore, exclusion of the latter is important.
- Other factors causing or aggravating cognitive decline should also be excluded.
- **Non-pharmacological approaches** to managing cognitive impairments include cognitive stimulation, use of memory aids, increased social interaction and stimulation, and exercise.

Cholinesterase Inhibitors

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  - Strategies for non-response or poor tolerance to one ChEI include switching to another ChEI.

- **Adverse effects**
  - Gastrointestinal symptoms
  - Postural hypotension
  - Urinary frequency
  - Hyper-salivation
  - Watering eyes
  - Runny nose
  - Worsening of extrapyramidal motor symptoms, particularly fine tremor.

  Adverse effects may improve with dose reduction.

Memantine

- **Consider as:**
  - monotherapy if cholinesterase inhibitors are not tolerated or contra-indicated.
  - in combination with cholinesterase inhibitors, particularly if the effectiveness of the cholinesterase inhibitor is limited or is declining, or the disease is becoming more severe.
- **Dose and titration**
  - Start at 5 mg daily and increase by 5 mg per week to a maximum of 20 mg daily if tolerated.
  - In patients with an estimated glomerular filtration rate (eGFR) of <50ml/min, dose adjustments maybe required.
- **Adverse effects**
  - Side effects of memantine include gastrointestinal symptoms, confusion, somnolence, hypertension and dizziness.
  - Be cautious in prescribing memantine to individuals with a history of **seizures**, or poor **renal function**.
  - May enhance the effects of **dopaminergics/selegiline**, and be toxic when given with **amantadine**.

- **Assessing response and deciding about continuation**
  - Record **baseline cognitive** performance using a preferred scale.
  - **Global** and **behavioural / psychiatric baseline** symptoms should also be documented.
  - Assess outcome after **3-6 months** on maximum tolerated dose (be aware that some patients may take longer to respond). Cognitive, global and other domain assessments may be used to support this.
  - Once optimised, treatment should be continued for as long as the patient/carer/clinician **consensus is that there are positive risk/benefits**.
  - Due to the progressive nature of LBD it is likely that global/behavioural/cognitive measures will eventually fall below baseline levels but this alone should not be taken as lack of continuing response.

Target Neurotransmitter	Drugs	Status	
		PD-MCI	PDD
Acetylcholine	Rivastigmine	Experimental	FDA-approved
	Donepezil		Off-label
	Galantamine		Off-label
NMDA	Memantine	Experimental	Experimental
	NYX-458		
	D-amino acid oxidase inhibitor (DAAOI-P)		Experimental
Dopamine	MAO-B inhibitors (e.g., rasagiline)	Investigational	
	Mevidalen (LY3154207) (D1 receptor positive allosteric modulator)		Experimental
Serotonin	SYN120 (dual 5-HT6/ 5-HT2A antagonist)		Experimental
Norepinephrine		Experimental	

Neurotransmitters targeted for pharmacologic treatments for Parkinson's Disease cognitive changes

BEHAV. SCI. 2021, 11, 54

Clinically available pharmacologic treatments for cognition in Parkinson's disease mild cognitive impairment and Parkinson's disease dementia

Category	Specific Agents	MCI	Dementia	Most Common Adverse Effects	Severe but Rare Adverse Effects
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

Behav. Sci. 2021, 11, 54

Agent	Treatment use	Comment
Dopaminergic agents	Motor dysfunction Cognitive impairment?	The benefits of dopaminergic agents in treating motor symptoms in PD are beyond question. However whether dopaminergic medications help or hinder cognitive function in PDD is controversial, and this uncertainty is reflected in the lack of understanding how dopamine function is perturbed in PDD. One open label study has suggested L-dopa or pergolide treatment in newly diagnosed PD may help improve cognition for a period [79].
Atomoxetine	Cognitive impairment?	A noradrenaline reuptake inhibitor with some evidence that it may help improve executive function in PD without dementia [80].
Safinamide	Cognitive impairment? Neuroprotective?	An agent with glutamatergic and dopaminergic effects and potentially neuroprotective qualities [81].
Amantadine	Neuroprotective?	An NMDA receptor antagonist which has been associated with reducing cognitive decline and delaying the onset of dementia in PD [82], and glutamate receptors have been suggested as potential targets for the development of novel pharmacological therapies for PD [83].

Examples of alternative pharmacological treatments in PDD

Common medications associated with adverse cognitive effects

Drug Class	Examples
Anticholinergics	
Tricyclic antidepressants	Amitriptyline, nortriptyline
First generation antihistamines	Diphenhydramine, hydroxyzine
Bladder antimuscarinics	Oxybutynin, trospium
Antipsychotics	Fluphenazine
Antimuscarinic spasmolytic	Atropine, hyoscyamine
Antiemetics	Meclizine
Muscle relaxants	Tizanidine
Anti-Parkinson	Benztropine, trihexyphenidyl
Benzodiazepines	Alprazolam, clonazepam, diazepam, lorazepam
Opioids	Codeine, hydrocodone, morphine, oxycodone, tramadol, methadone, fentanyl

Autonomic Symptoms

Autonomic Symptoms

Urinary Dysfunction

- **Non-pharmacological (first line) treatment of urinary incontinence**
  - **Regular, prompted, voiding** with use of incontinence pads may be helpful.
  - Consider **referral** to an incontinence nurse and/or urology if symptoms are particularly troublesome or have never been previously investigated.
- **Pharmacological treatment of urinary incontinence**
  - **Avoidance or reduction in diuretics** may help if no contraindications.
  - Be aware that cholinesterase inhibitors can precipitate urgency and urge incontinence.
  - **Avoid: Bladder anticholinergics** particularly the use of agents which have a significant centrally acting effect such as oxybutynin and tolterodine.
  - Intravesical botulium toxin may have a positive effect on neurogenic detrusor overactivity in those intolerant of anticholinergics.
  - Mirabegron, a β3 adrenergic agonist (25-50 mg per day) may be an alternative to anticholinergics for bladder overactivity.

Male sexual dysfunction

- The use of phosphodiesterase-5 inhibitors such as sildenafil can be considered for erectile dysfunction; prescribe with caution if the patient has postural / orthostatic hypotension.

Excessive sweating

- Wear loose fitting/natural fibre clothing and use natural light cotton bedding if there are significant night sweats. Antiperspirants can help some.
- Avoid foods and situations which trigger sweating e.g. alcohol, spicy foods, hot rooms.
- Ensure adequate fluid intake to replace losses.
- Alteration to the dopamine replacement regimen may sometimes help if associated with "OFF" motor state.

Constipation

- Check there has been no significant changes in bowel habits (such as per rectum bleeding, weight loss and/or anaemia) which may indicate other causes.
- Give advice on fluid and fibre intake, as well as exercise.
- If possible avoid constipating medications (e.g. opiates and some anti-parkinsonian drugs).
- Stool softeners can be helpful if stools are very hard.
- Mild suppositories such as glycerine may help also bowel emptying.
- Laxatives can be used, if required e.g.
  - Senna (7.5-15 mg at night)
  - Bisacodyl (5-10 mg at night)
  - Sodium docusate (50-400 mg in divided doses each day)
  - Bulk forming / osmotic laxatives e.g. macrogol.
- Lubiprostone is a second line treatment: 24 mcg twice daily.

Sialorrhoea

- Speech and language therapist input can be helpful.
- Use of sugar free chewing gum or boiled sweets may help some.
- Anticholinergics should not be used if possible.
- Botulinum toxin injections to salivary glands is an effective treatment.
- Clonidine 150 mcg per day is an alternative option, but can aggravate orthostatic hypotension and precipitate daytime somnolence.
- Glycopyrrolate 1–2 mg twice or three-times daily is a second line option.

Gastroparesis

- Be aware that dopaminergic medications can exacerbate gastroparesis.
- Advise the patient to have small and frequent meals and drink during meals. Avoidance of high fat foods may also help as well as walking after meals.
- Domperidone (10-20 mg three times daily) has been used to treat gastroparesis but there are significant concerns with regard to cardiotoxicity and the risk of QTc prolongation. If risk of QTc prolongation will need ECG before starting and after one week of treatment. If prescribed longer term will need regular review.
- Avoid using metoclopramide given its central dopamine antagonist effect.
- Giving levodopa in solution may help with patients with significant motor fluctuations and delayed gastric emptying.
- Alternatively, for some patients with delayed gastric emptying, their motor fluctuations may be improved through jejunal administration of levodopa.

Orthostatic hypotension

- Medications (e.g. levodopa, dopamine agonists, antihypertensives, antidepressants, alpha-adrenergic blockers, sildenafil), dehydration, cardiac disease, fever and anaemia may cause or exacerbate orthostatic hypotension.
- Orthostatic hypotension may manifest at particular times e.g. at mealtimes, when taking alcohol, in early morning, during defecation or micturition, and/or with physical activity.
- If there is **significant dizziness, falls or episodes of loss of consciousness**, **consider a referral** to a falls/ syncope clinic.
- **Non-pharmacological principles (first line)**
  - Advise the patient to stand slowly
  - Raising the head of the bed may help with morning orthostatic hypotension.
  - Slight increases in salt intake may help some
  - Consider use of compression hosiery
  - Increase fluid intake – usual advice is 2 litres, in total, daily.
- Potential **pharmacological therapies**
  - Fludrocortisone (50-300 mcg/ day). Titrate slowly and monitor electrolytes
  - Midodrine (2.5-10 mg bd). Monitor hepatic and renal function (needs specialist to initiate)
  - Note: these medications for orthostatic hypotension may cause severe supine hypertension and thus regular monitoring of blood pressure is needed.

Sleep Disturbances

Sleep Disturbances

Excessive daytime sleepiness

- Document the frequency and occurrence of daytime sleepiness. Sleep scales may be helpful.
- Give advice on sleep hygiene and treat any sleep disturbances.
- Exclude physical and medication causes.
- There are no specific pharmacological interventions but cholinesterase inhibitors may improve sleepiness in some. Psychostimulants, if used, should be prescribed by a specialist experienced in their use.

Restless legs syndrome (RLS)

- Be aware may be due to other factors e.g. anaemia, diabetes or renal dysfunction. **In particular clinicians should consider checking ferritin levels** in appropriate patients, and in those with values < 50 ug/mL, to recommend oral iron replacement therapy for at least two to three months.
- Some medications e.g. antidepressants, antipsychotics and anti-emetics may exacerbate RLS.
- Regular exercise may help.
- Avoid smoking.
- **Pharmacological treatments** include:
  - Dopamine replacement therapy
  - Gabapentin

A **high degree of caution** needs to be applied if using these drugs given their potential for side effects.

Motor-related sleep disturbances

- Noctural extrapyramidal symptoms may be improved using long acting levodopa preparations prior to going to bed.
- Be aware though of their propensity to cause side effects e.g. neuropsychiatric.

Sleep apnoea

- Be **aware of risk factors** (overweight, male, smoker, on sedatives, alcohol use, reflux and anatomical considerations e.g. collar size >43 cm or 17 inches).
- If suspicion of sleep apnoea, consider referral to a sleep centre.
- Continuous positive airways pressure (CPAP) treatment in confirmed sleep apnoea can improve nocturnal sleep, cognition and daytime sleepiness.

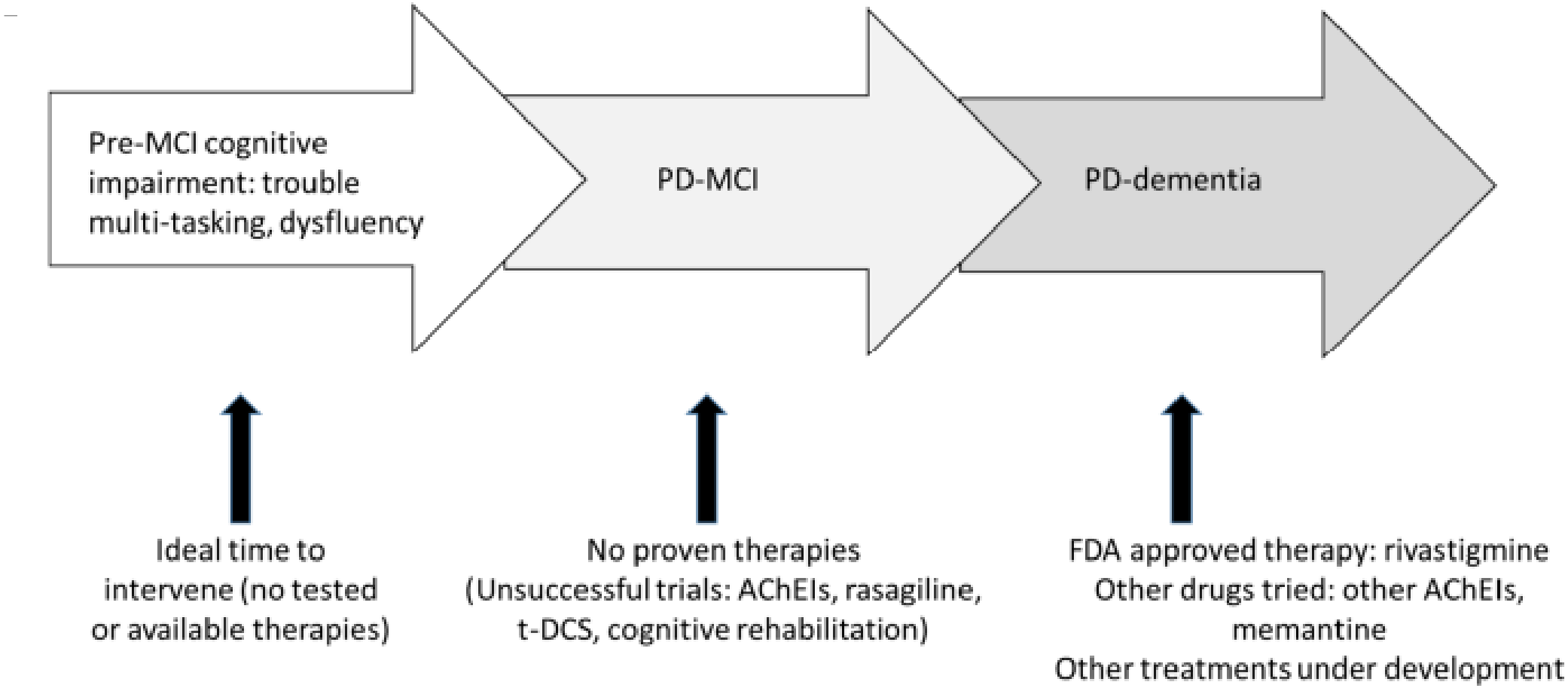
REM-sleep behaviour disorder

- Consider and exclude potential mimics e.g. obstructive sleep apnoea
- **Consider non-pharmacological strategies as a first line, for example:**
  - placing bed on floor,
  - removing potentially dangerous objects and put padding around sharp/firm objects,
  - bed partners sleep separately etc.
- **Pharmacological treatments**
  - Clonazepam 250 mcg – 500 mcg (up to 1000 mcg) per day taken 30 minutes before bedtime. Be aware of side effects esp. increased risk of falls/worsening cognition.
  - Melatonin 3 mg to 12 mg per day taken before bedtime. Despite lack of evidence used by some as first line treatment given relatively benign side effect profile.
- Be aware some medications may exacerbate REM-sleep behaviour symptoms.

Insomnia & sleep fragmentation

- Advise on good **sleep hygiene**:
  - avoidance of stimulants in late afternoon/evening e.g. caffeine
  - avoid alcohol in the evening
  - establish regular pattern of sleep
  - have comfortable bedding and temperature
  - restrict daytime naps, and
  - take regular exercise.
- **Review of all medication** and avoid any drugs that may affect sleep or alertness, or may interact with other medication.
- Treat nocturia if a cause is identified. **Avoid anticholinergics** if possible.
- Melatonin 3 to12 mg before bedtime may help some with subjective sleep disturbance.
- Zopiclone and zolpidem may be options short-term but have the potential for significant side effects.

Approach to treating cognitive impairment in Parkinson's disease



Behav. Sci. 2021, 11, 54

Difference between Parkinson's Disease Dementia (PDD) and Dementia with Lewy Bodies (DLB)

PARKINSON'S DISEASE DEMENTIA	DEMENTIA WITH LEWY BODIES
When the person experiences dementia symptoms a year or more after motor symptoms appear, the diagnosis is Parkinson's disease dementia.	When the person experiences dementia symptoms before, at the same time as, or within one year after motor symptoms appear, the diagnosis is dementia with Lewy bodies.

Summary of Differences between DLB and PDD

Differences	DLB	PDD
Dementia onset relative to parkinsonism	earlier	later
Executive dysfunction	+++	++
Cognitive fluctuations	+++	++
Psychotic symptoms	+++	++
Levodopa responsiveness	+	++
Parkinsonism	≈25–50% – less tremor	100%
Pathology		
Cortical amyloid load	++	+
Nigral cell loss	+	+++
Alpha-synuclein deposition in striatum	+++	+

THANK YOU