COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

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PARKINSON'S DISEASE

- Second commonest neurodegenerative disorder
- Affects >1% of individuals over 65 years
- Diagnosis is based on the cardinal motor features:
  - Bradykinesia
  - Rigidity
  - Rest tremor
- But, not just a motor disorder!
- Many non-motor symptoms exist which often affect the individual as much as, if not more than, the motor symptoms

“OFF” MEDICATIONS

“ON” MEDICATIONS

NATURAL HISTORY OF PD

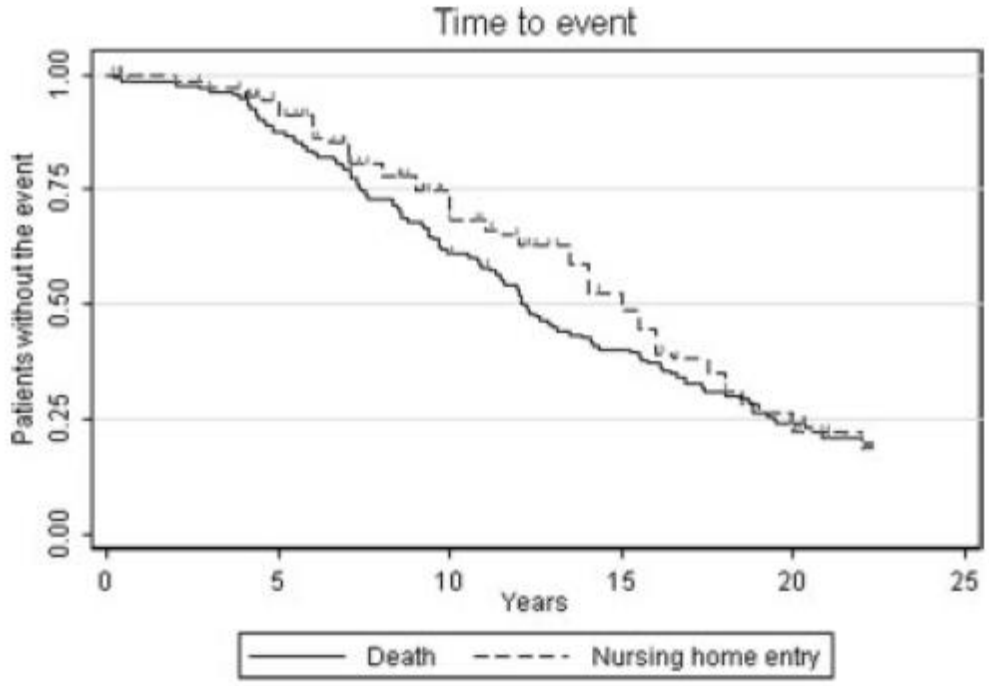


FIG. 1. Kaplan–Meier plot of time to death and of nursing home placement.

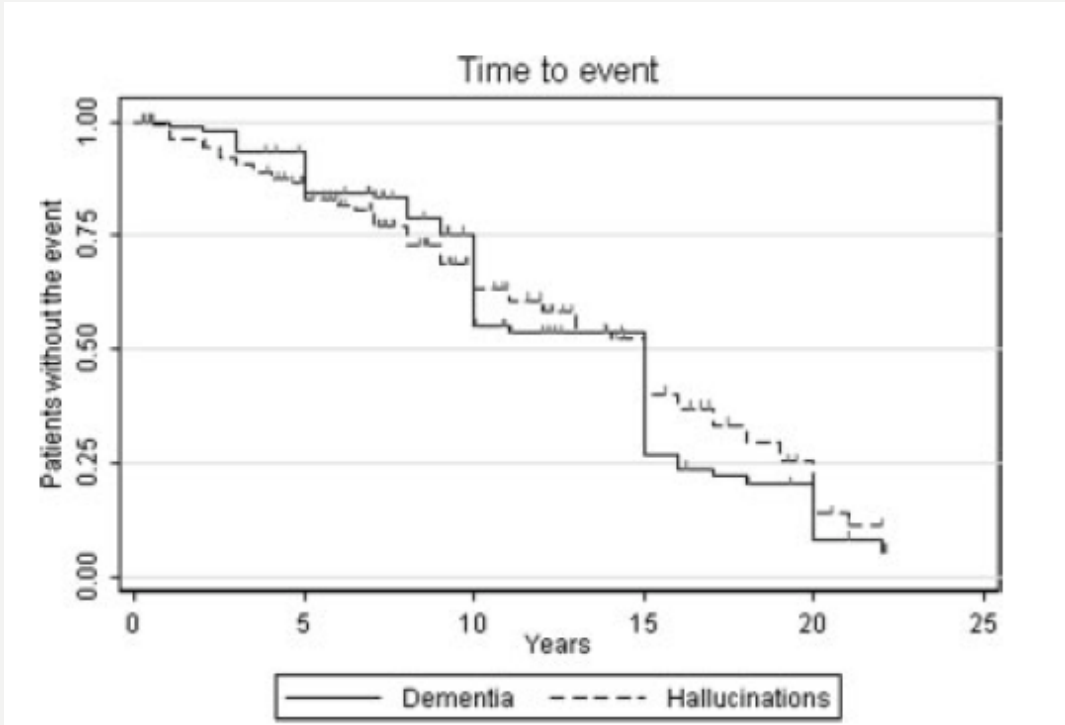
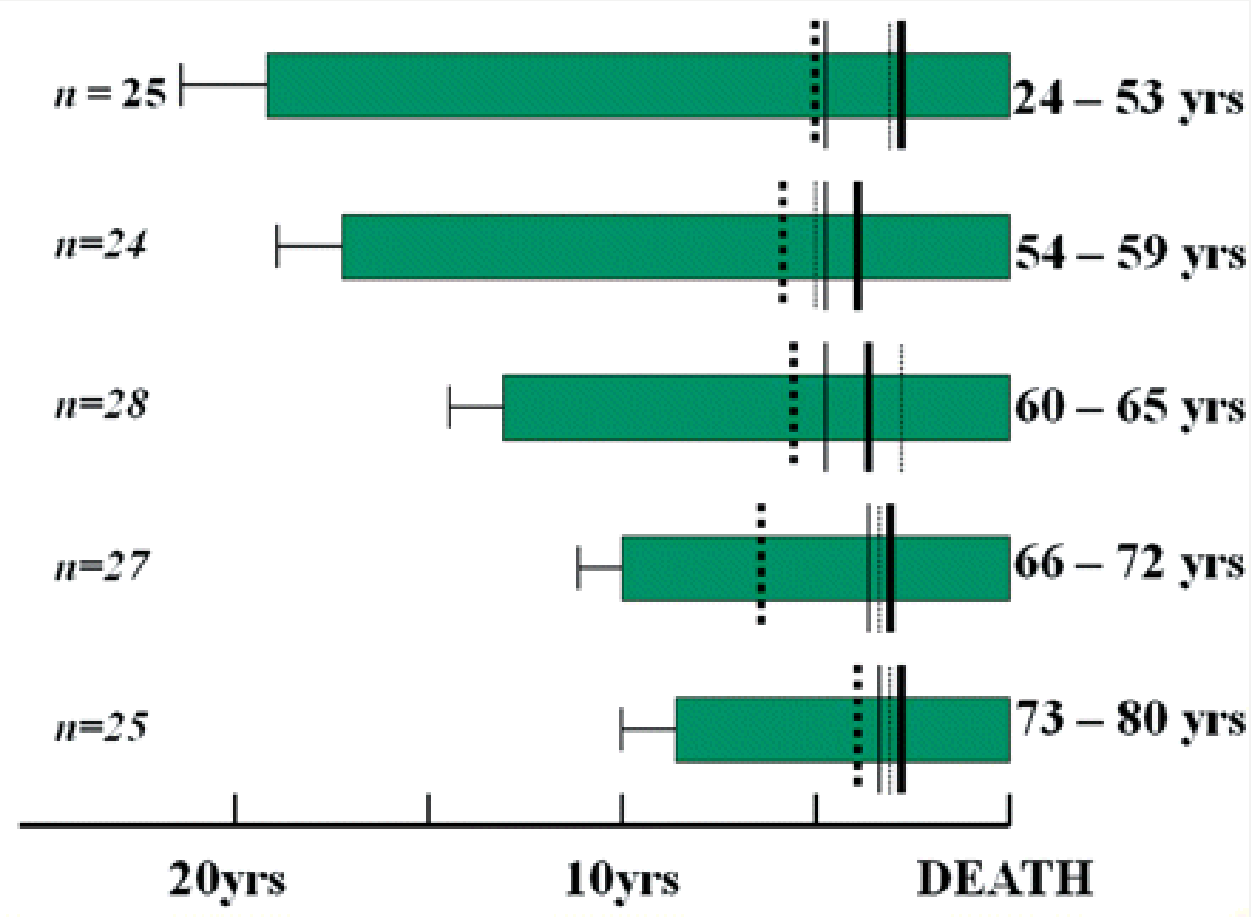


FIG. 3. Kaplan–Meier plot of time to hallucinations and dementia.

Hely, M. A., Reid, W. G. J., Adena, M. A., Halliday, G. M., & Morris, J. G. L. (2008). The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. *Movement Disorders, 23(6), 837-844. doi:doi:10.1002/mds.21956*

Natural Progression of Parkinson's Disease



Regular falls = fine lines; residential care = heavy lines; cognitive disability = fine dots; visual hallucinations = heavy dots. Error bars show the standard error of the mean disease duration.

Brain, Volume 133, Issue 6, June 2010, Pages 1755–1762, https://doi.org/10.1093/brain/awq059

COGNITIVE IMPAIRMENT

- Typically slow in Parkinson's disease
- Spectrum of cognitive decline:
  - Subjective cognitive decline: perceived decline in cognition with normal performance on cognitive testing
  - Mild cognitive impairment (PD-MCI): gradual decline in cognition associated with cognitive deficits on formal testing. Can be classified as single or multiple domain.
  - PDD:
    - Deficits in at least 2 of 4 domains (executive function, attention, visuospatial abilities, memory) severe enough to affect normal function
    - Can be mild (mild effect on daily function), moderate, or severe (unable to live independently)
  - DLB:
    - Dementia occurring before or within 1 year onset of motor features of PD

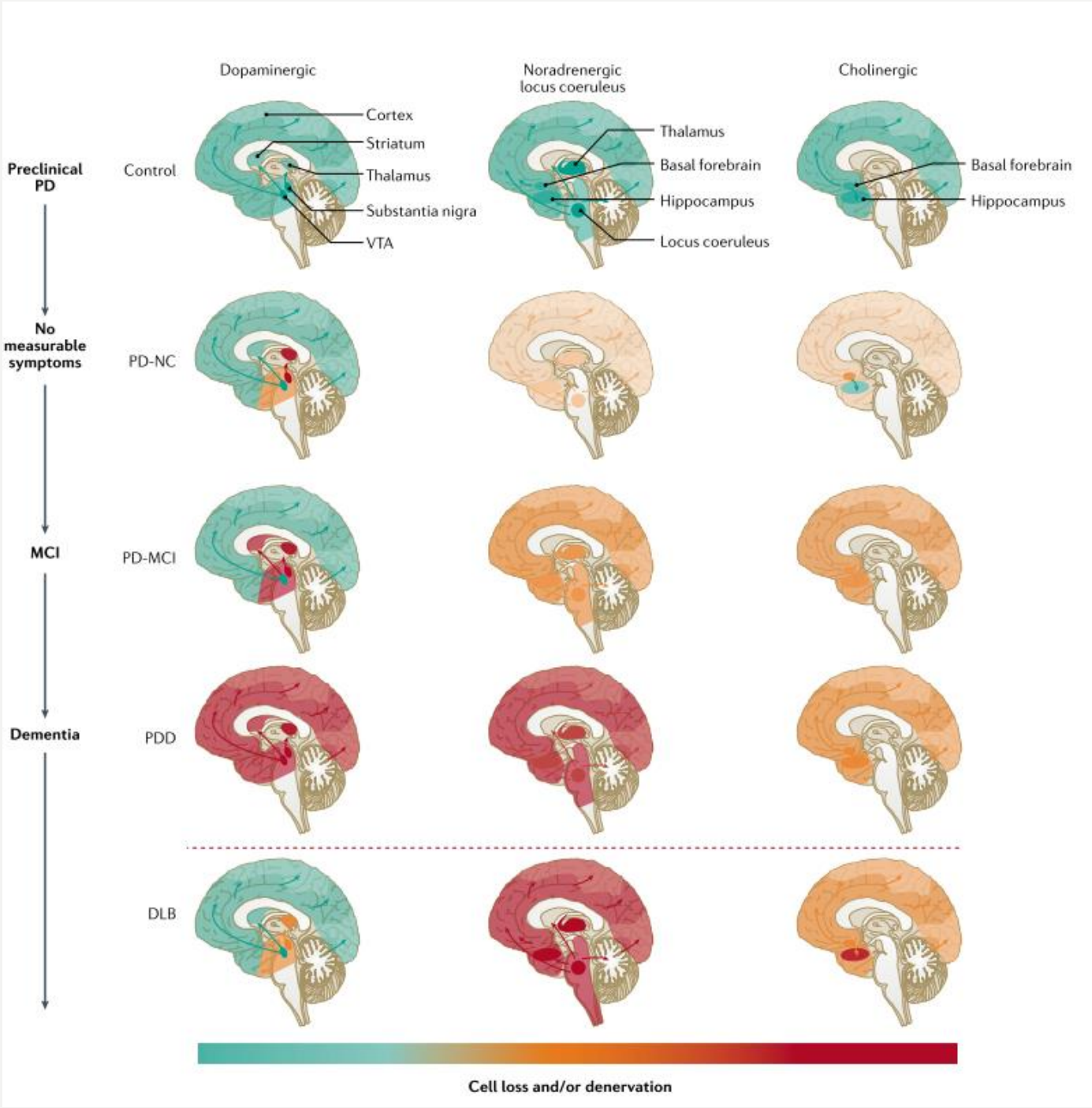
DOMAINS INVOLVED

- Typically multiple cognitive domains are affected:
  - Memory
  - Attention
  - Visuospatial abilities
  - Executive function

LEWY BODY DEMENTIAS

- Lewy bodies:
  - First described in 1912 by Frederick Lewy, to be present in substantia nigra in PD
  - In 1961, cortical Lewy bodies were identified and found to be associated with dementia
  - Seen in various diseases, including: PD, DLB, MSA, PDD
- PDD and DLB are remarkably similar, despite differing temporal onset of cognitive impairment
- At autopsy, there are widespread limbic and cortical Lewy bodies; brainstem, cortical and limbic Lewy neurites, loss of dopaminergic cells in the midbrain; and loss of cholinergic neurons in ventral forebrain nuclei
- AD pathology is found in the majority of cases also

PATHOLOGY


Dopaminergic
Noradrenergic
locus coeruleus
Cholinergic
Cortex
Striatum
Thalamus
Substantia nigra
VTA
Thalamus
Basal forebrain
Hippocampus
Locus coeruleus
Basal forebrain
Hippocampus
Preclinical PD
Control
No measurable symptoms
PD-NC
MCI
PD-MCI
Dementia
PDD
DLB
Cell loss and/or denervation

PREVALENCE

- Up to 6 times more common than in healthy individuals
- DLB:
  - Affects 1-2% of population >65 years
  - Accounts for ~5% of all dementia >75 years
- Dementia prevalence in PD increases with disease duration (NB: global prevalence 5-7% >60 years):
  - 17% at 5 years
  - 46% at 10 years
  - 83% at 20 years

RISK FACTORS FOR DEVELOPING COGNITIVE IMPAIRMENT OR DEMENTIA

- Hallucinations
- Older age
- Severity of motor symptom
- Speech impairment
- Older age at PD onset
- Severity of bradykinesia
- Axial impairment
- Low level of education
- Depression
- Male

DIAGNOSIS AND SCREENING

- Diagnosis based on formal neuropsychological assessment or evaluation of global cognition
- Screening:
  - MoCA: most frequently used and recommended
    - Cut off of 23/24 has specificity of 0.82 and sensitivity of 0.41
  - Mattis Dementia Rating Scale Second Edition (MDRS-2)
  - Parkinson's Disease – Cognitive Rating Scale (PDCRS)

PARKINSON'S DISEASE DEMENTIA

COGNITIVE IMPAIRMENT IN PD

- Must have had a diagnosis of PD prior to the onset of definite cognitive decline
- Often seen at presentation, however the predominant issues are motor abnormalities
- Cognitive impairment increases with disease duration and severity
- Dementia in PD has been shown to be associated with morbidity and mortality, with studies showing the onset of dementia ~5 years prior to death

COGNITIVE SYMPTOMS

- Domains affected:
  - Impaired attention (may fluctuate)
  - Executive dysfunction
  - Memory:
    - Recall is impaired, though with prompting can improve
  - Visuospatial issues
  - Language typically preserved
- Issues with medications, finances, attention, multi-tasking
- Bradyphrenia is common
- Visual hallucinations can be seen (need to ensure not medication related, e.g., dopamine agonists)

BEHAVIOURAL SYMPTOMS

- Mood disturbance:
  - Depression
  - Anxiety
- Apathy
- Irritability
- Hallucinations

DIAGNOSIS: PD-MCI

Box 1 | **Movement Disorder Society PD-MCI diagnostic criteria**[7,120]

Level I – Abbreviated assessment

- Impairment on Parkinson disease (PD)-appropriate global cognitive ability scale (such as Montreal Cognitive Assessment (MoCA), Parkinson's Disease – Cognitive Rating Scale (PD-CRS), Mattis Dementia Rating Scale Second Edition (MDRS-2))
- Impairment on at least two neuropsychological tests when a limited set of tests is used (less than two tests per domain or less than five cognitive domains assessed)

Level II – Comprehensive assessment

- Neuropsychological testing includes two tests per domain:
  - Attention and working memory
  - Executive functions
  - Language
  - Memory
  - Visuospatial skills
- Impairment on two tests in one domain or impairment on one test in two different domains
- Impairment shown by:
  - Score 1–2 SD below norm
  - Significant decline on serial testing
  - Significant decline from estimated premorbid functioning

PD with mild cognitive impairment (PD-MCI) subtype classification (comprehensive level II assessment required)

- Single domain: impairment on two or more tests in one domain
- Multiple domain: impairment on at least one test in each of two or more domains

DIAGNOSTIC CRITERIA FOR PDD

TABLE 1. *Features of dementia associated with Parkinson's disease*

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
   - Impairment in more than one cognitive domain
   - Representing a decline from premorbid level
   - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

1. Cognitive features:
   - Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
   - Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
   - Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
   - Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
   - Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
2. Behavioral features:
   - Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
   - Changes in personality and mood including depressive features and anxiety
   - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
   - Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
   - Excessive daytime sleepiness

III. Features which do not exclude PD-D, but make the diagnosis uncertain

- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
- Time interval between the development of motor and cognitive symptoms not known

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D

- Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:

  Acute confusion due to
  a. Systemic diseases or abnormalities
  b. Drug intoxication

  Major Depression according to DSM IV
- Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

DIAGNOSTIC CRITERIA FOR PDD

TABLE 2. *Criteria for the diagnosis of probable and possible PD-D*

Probable PD-D

A. Core features: Both must be present

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 memory which usually improves with cueing)
- The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis

C. None of the group III features present

D. None of the group IV features present

Possible PD-D

A. Core features: Both must be present

B. Associated clinical features:

- Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
- Behavioral symptoms may or may not be present

OR

C. One or more of the group III features present

D. None of the group IV features present

Emre, M., Aarsland, D., Brown, R., Burn, D. J., Duyckaerts, C., Mizuno, Y., . . . Dubois, B. (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders, 22*(12), 1689-1707.

DIAGNOSIS: PDD

Box 2 | **Diagnostic procedure Movement Disorder Society PDD criteria**[8,144]

Level I — Parkinson disease dementia (PDD)

- A diagnosis of Parkinson disease (PD) based on the UK Brain Bank criteria for PD
- PD developed prior to the onset of dementia
- Mini-Mental State Examination (MMSE) below 26
- Cognitive deficits severe enough to impact daily living (caregiver interview or Pill Questionnaire) independent of motor symptoms
- Impairment in more than one cognitive domain, that is, at least two of the following aspects:
  - Months Reversed or Seven Backward
  - Lexical Fluency or Clock Drawing
  - MMSE Pentagons
  - Three-Word Recall
- Absence of major depression
- Absence of delirium
- Absence of other abnormalities that obscure diagnosis

Level II — Comprehensive assessment for characterizing PDD

The level II evaluation assesses four domains:

- Decreased global cognitive efficiency
- Subcorticofrontal features of PDD
- Instrumental (cortically mediated) functions:
  - Language
  - Visuoconstructive
  - Visuospatial
  - Visuoperceptive
- Neuropsychiatric features:
  - Apathy
  - Depression
  - Visual hallucination
  - Psychosis

DEMENTIA WITH LEWY BODIES

COGNITIVE SYMPTOMS

- Fluctuating cognition
- Fluctuating attention and arousal
  - Increasing daytime drowsiness
  - Staring
- Early dementia
- Usually early hallucinations
- Parkinsonism can either develop in parallel or shortly thereafter
- Multiple domains can be affected:
  - Memory
  - Visuospatial
  - Executive function – difficulty dual tasking
  - Attention

NEUROPSYCHIATRIC SYMPTOMS

- Complex visual hallucinations are common early in disease
  - Usually well formed; e.g., people, animals
  - Initially not intrusive, though can become so
- Visual illusions:
  - Especially at night/ spaces with reduced light
  - E.g., insects on wall; lamp thought to be a person
- Delusions:
  - Typically later in disease course
  - Paranoid delusions; e.g., spouse having an affair, people stealing from them
  - Capgras syndrome: caregiver replaced by an imposter

SIGNS

- Parkinsonism
  - Variable presentation, from classic iPD to more symmetrical signs
  - May not respond to levodopa as well as classic iPD
  - Imaging identifies dopaminergic activity (reduced DAT) on SPECT and PET
- Neuroleptics
  - May have increased sensitivity to neuroleptics (e.g., NMS), and these must be avoided! (e.g., haloperidol)

SIGNS

- RBD
  - Can predate the onset of other features by many years
- Autonomic impairment
  - Constipation
  - Orthostatic hypotension can occur
  - Urinary frequency/ incontinence

DIAGNOSTIC CRITERIA

Table 1 Revised[1,2] criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)

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.

Probable DLB can be diagnosed if:

a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or

b. Only one core clinical feature is present, but with one or more indicative biomarkers.

Probable DLB should not be diagnosed on the basis of biomarkers alone.

Possible DLB can be diagnosed if:

a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or

b. One or more indicative biomarkers is present but there are no core clinical features.

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. The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism continues to be recommended.

McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J.-P., Weintraub, D., . . . Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology, 89*(1), 88-100.

INVESTIGATION

- Exclude other causes:
  - Concomitant infection
  - Medications: anticholinergics, dopamine agonists, amantadine
  - Serological testing: TFT, B12, metabolic, infectious and autoimmune markers
  - MRI brain to investigate structural causes
  - EEG: to investigate for seizure activity
- Biomarkers:
  - MRI:
    - Temporoparietal atrophy: classically seen with AD pathology
    - Basal forebrain atrophy
  - FDG-PET:
    - Hypometabolism in medial frontal and parietal regions -> decline in executive and memory function, but not specific
  - DAT imaging: reduced DAT levels seen in PDD and DLB (and not AD). Also seen in CBS and PSP
- CSF:
  - Some utility in AD biomarkers amyloid/tau
  - No definitive evidence of CAF alpha-synuclein

MANAGEMENT

- Medication rationalisation:
  - Weaning and ceasing non-levodopa medications
  - Including: anti-cholinergic, amantadine, dopamine agonists, COMT-I
- Treat comorbidities:
  - Obstructive sleep apnoea
  - Orthostatic hypotension
  - Depression/ anxiety
  - Psychosis
  - RBD
  - Vascular risk factors

MANAGEMENT: COGNITIVE IMPAIRMENT

- Acetylcholinesterase inhibitors:
  - Rivastigmine:
    - Only positive study to date for PDD
    - Modest improvement reported in cognition
    - Transdermal may be more tolerable than oral
  - Donepezil:
    - PDD: improvement in cognition, but not statistically significant
    - DLB: improvement seen in one RCT in Japan
  - Galantamine: possibly useful, but requires more evidence
  - Memantine: possibly useful (especially in DLB), but requires further evidence
  - Transcranial stimulation: remains under investigation
  - Creatine and CoQ10: when used together, rate of cognitive decline was reduced at 12 and 18 months (using serial MoCA)
- No treatment exists for PD-MCI

MANAGEMENT: PSYCHOSIS

- Pimavanserin:
  - No significant dopamine blocking properties
  - RCT evidence to reduce psychotic symptoms in PD psychosis
  - Can take 4-6 weeks to take effect
  - Secondary benefit includes improved nighttime sleep and excess daytime sleep
  - Not available in Australia
- Quetiapine:
  - Typically used as first line for psychotic symptoms in PD
  - However, randomised trials have not supported the widespread use, with limited evidence

MANAGEMENT: PSYCHOSIS

- Clozapine:
  - Minimal extrapyramidal side effects
  - Reduces psychotic symptoms compared with placebo
  - Side effects limit its use, including agranylocytosis (needs frequent monitoring with blood tests); also requires initiation and continuation in consultation with a psychiatrist
- Acetylcholinesterase inhibitors:
  - Some evidence of reduction in psychotic symptoms, especially hallucinations
  - Rivastigmine is most commonly used and reported as beneficial

MANAGEMENT

- Parkinsonism:
  - Levodopa
  - Physiotherapy
  - Occupational therapy
- Depression:
  - Sertraline
  - Venlafaxine XR
  - Mirtazapine
- Apathy:
  - Acetylcholinesterase inhibitors
  - SSRIs

MANAGEMENT

- Insomnia:
  - Melatonin
  - Mirtazapine
  - Quetiapine
- RBD:
  - Melatonin
  - Clonazepam
- Constipation:
  - Important to treat!
  - Movicol + fibre supplement

MANAGEMENT

- Non-pharmacological measures:
  - Limited evidence:
    - Cognitive interventions
    - Physical exercise
  - Insufficient evidence:
    - Non-invasive brain stimulation: transcranial direct current stimulation or repetitive transcranial magnetic stimulation
    - Deep brain stimulation (invasive)

PLANNING

- Important to be open and honest with patient, family and carers
- Discuss future planning, including:
  - Finalising will
  - Advanced care directive
  - Guardianship (if needed)
  - NDIS/ACAT
- In later stages, consider involvement of palliative care team

SUMMARY

- Lewy body disease encompasses multiple entities, including PD, PDD and DLB
- PDD and DLB have similar features, with an arbitrarily defined time of dementia vs Parkinsonism onset
- PDD and DLB likely are on a spectrum of the same disease entity
- Management is aimed at the underlying symptoms, including cognitive impairment, psychotic symptoms, sleep disturbance, and Parkinsonism