HSTalks

Prof. John-Paul Taylor – Newcastle University, UK

Lewy Body Dementia

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Lewy body dementia

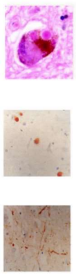
Lewy body dementia includes both:

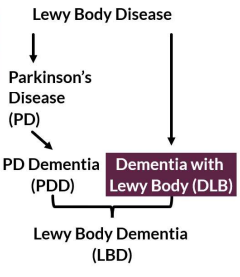
Parkinson's disease dementia (PDD)

Dementia starting 1 year or more after well established Parkinson's disease

Dementia with Lewy bodies (DLB)

Dementia that occurs before or concurrently with parkinsonism or within 1 year of onset of motor symptoms





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DLB underdiagnosis and lack of a systematic approach to management

- Post-mortem examination indicates that 15–20% of dementia cases have evidence of Lewy body disease
- Clinical DLB diagnostic rates from selected cohorts are much lower, 4–7%, than expected from autopsy studies (Vann-Jones and O'Brien, 2014), but diagnostic rates in routine clinical practice is unknown
- Previous studies suggest under-recognition and a more complex road to diagnosis (Galvin *et al.*, 2010)

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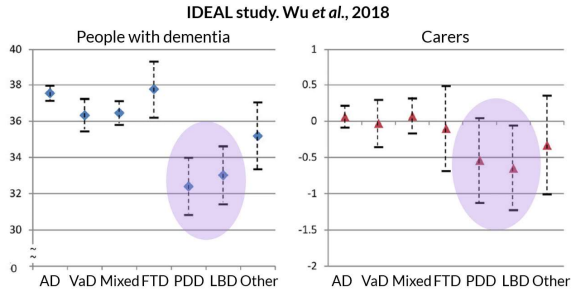
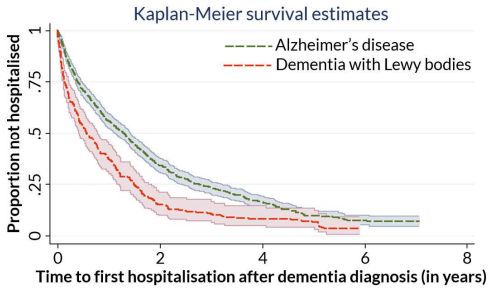
DLB underdiagnosis and lack of a systematic approach to management

Lowest quality of life in LBD



Very poor outcomes in DLB



Significantly higher acute hospital resource use in DLB than AD (Mueller *et al.*, 2018)

Images courtesy of Christoph Mueller & Annabel Price

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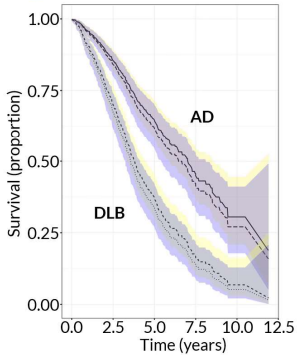
Very poor outcomes in DLB

- **AD survival:**
  Males: 6.7 years;
  Females: 7.0 years
- **DLB survival:**
  Males: 3.3 years;
  Females: 4.0 years

Price *et al.*, 2017



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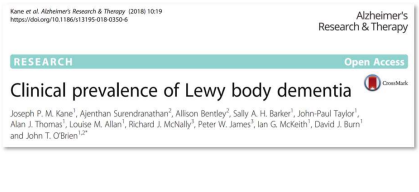
Prevalence of DLB in the UK



Alzheimer's Research & Therapy

RESEARCH Open Access

Clinical prevalence of Lewy body dementia

Joseph P. M. Kane[1], Ajenthan Surendranathan[2], Allison Bentley[2], Sally A. H. Barker[1], John-Paul Taylor[1], Alan J. Thomas[1], Louise M. Allan[1], Richard J. McNally[3], Peter W. James[3], Ian G. McKeith[1], David J. Burn[1] and John T. O'Brien[1,2*]

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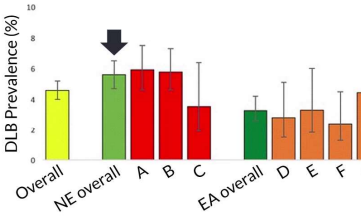
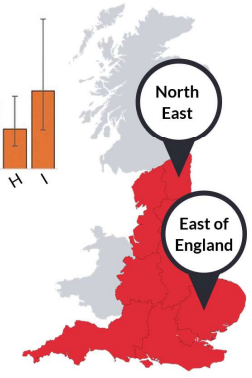
Prevalence of DLB in the UK

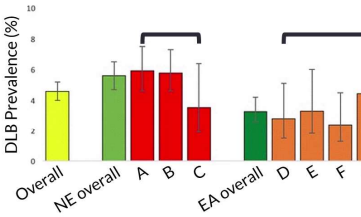


Patients with DLB comprised 4.6% of all dementia cases

DLB prevalence was higher in North-East England (p<0.01)



Prevalence of DLB in the UK



2.4% to 5.9% range in individual services: a significant variation in services (p<0.05)

There is a need to raise the profile of DLB as well as understanding of how a diagnosis can be made

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Clinical diagnostic criteria

Core clinical features	Supportive clinical features
Indicative biomarkers	Supportive biomarkers

McKeith I.G., *et al., Neurology.* 2017; **89**(1): 88-100

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Clinical diagnostic criteria

Diagnosis of probable DLB:			Diagnosis of possible DLB:	
Core clinical features x2	or	Core clinical features x1	Core clinical features	x1
		Indicative biomarkers x1	Indicative biomarkers	x1

McKeith I.G., *et al., Neurology.* 2017; **89**(1): 88-100

Clinical diagnostic criteria

Core clinical features	Supportive clinical features
Indicative biomarkers	Supportive biomarkers

McKeith I.G., *et al., Neurology.* 2017; **89**(1): 88-100

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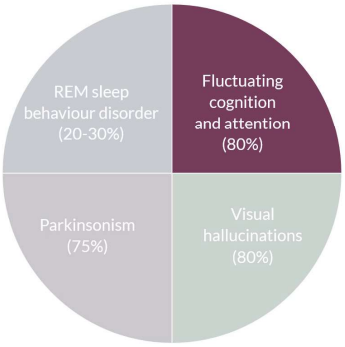
Core clinical features: fluctuating cognition



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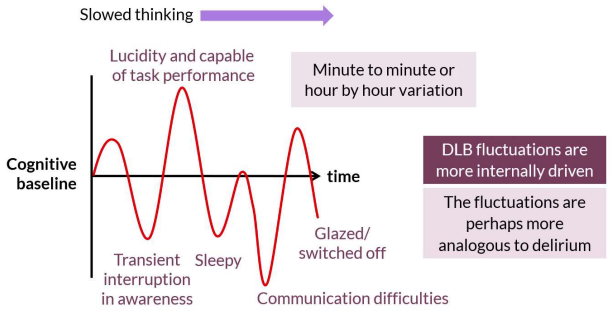
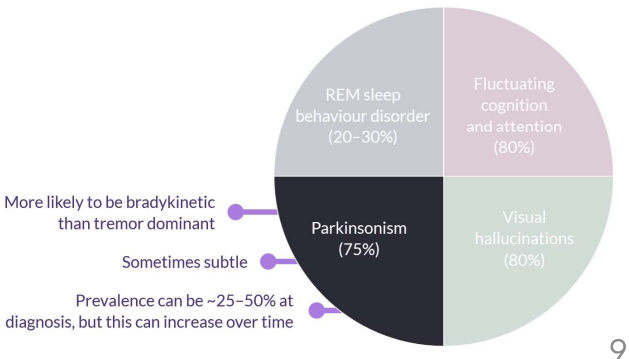
Core clinical features: fluctuating cognition

Fluctuating cognition and attention (80%)



Core clinical features: Parkinsonism



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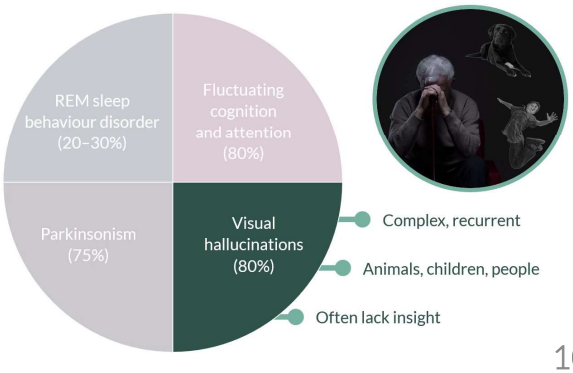
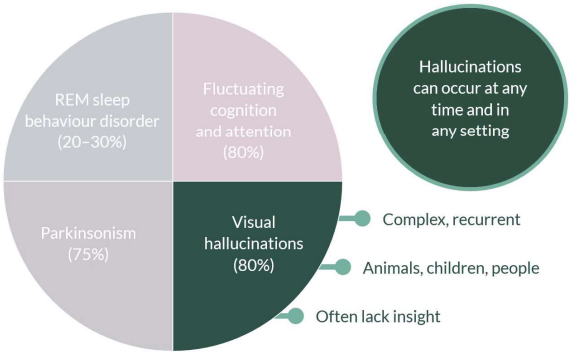
Core clinical features: visual hallucinations

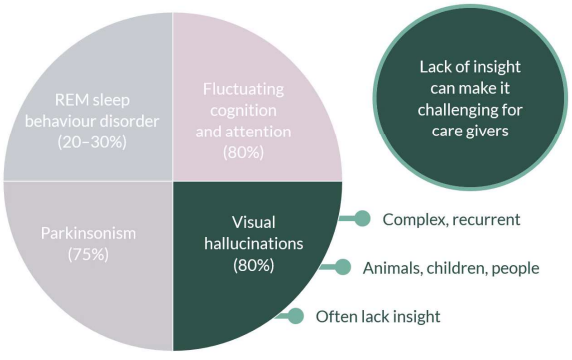


10

Core clinical features: visual hallucinations



Core clinical features: visual hallucinations



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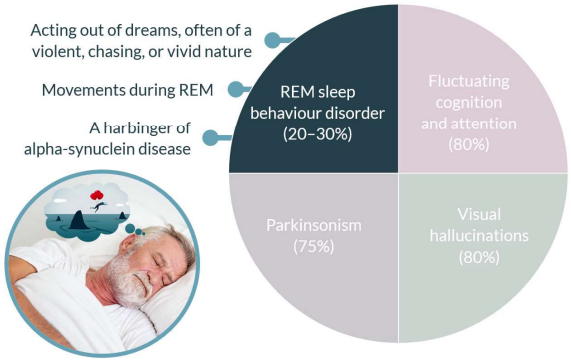
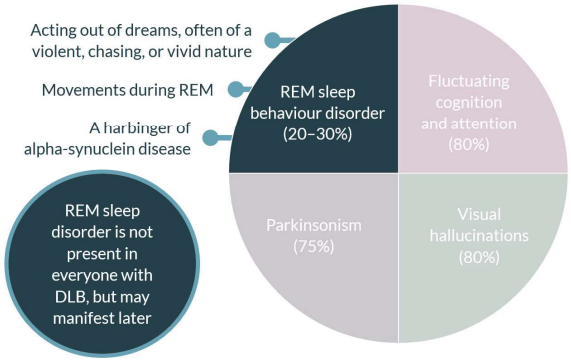
Core clinical features: REM sleep behaviour disorder



11

Core clinical features: REM sleep behaviour disorder



Clinical diagnostic criteria

Core clinical features	Supportive clinical features
Indicative biomarkers	Supportive biomarkers

McKeith I.G., *et al., Neurology*. 2017; **89**(1): 88-100

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Clinical diagnostic criteria: supportive clinical features

Severe antipsychotic sensitivity	Hypersomnia
Postural instability and repeated falls	Hyposmia
	Hallucinations in other modalities
Syncope or other transient episodes of unresponsiveness	Systematised delusions
Severe autonomic dysfunction	Depression, anxiety, apathy

McKeith I.G., *et al., Neurology.* 2017; **89**(1): 88-100

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Clinical diagnostic criteria

Core clinical features	Supportive clinical features
Indicative biomarkers	Supportive biomarkers

McKeith I.G., *et al., Neurology.* 2017; **89**(1): 88-100

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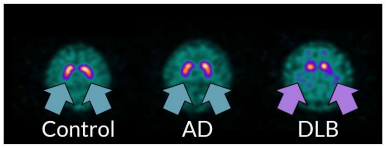
Indicative biomarkers

1

Dopamine transporter imaging

An indirect measure of the integrity of the nigrostriatal system which is disrupted in DLB



Excellent sensitivity and specificity for DLB

McKeith I.G., *et al., Neurology.* 2017; **89**(1): 88-100

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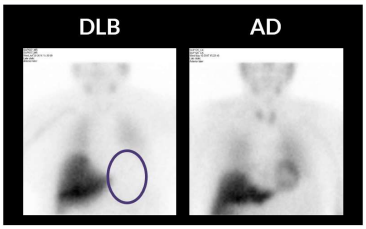
Indicative biomarkers

2

MIBG imaging

Cardiac scintigraphy using MIBG to look at cardiac sympathetic drive



McKeith I.G., *et al., Neurology.* 2017; **89**(1): 88-100

Indicative biomarkers

3

Polysomnography

The gold standard way to diagnose the presence of REM sleep behaviour disorder where EEG, EOG and video telemetry are used

McKeith I.G., *et al., Neurology.* 2017; **89**(1): 88-100

Clinical diagnostic criteria

Core clinical features	Supportive clinical features
Indicative biomarkers	Supportive biomarkers
	Some of these lack the same diagnostic accuracy as indicative biomarkers

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McKeith I.G., *et al., Neurology.* 2017; **89**(1): 88-100

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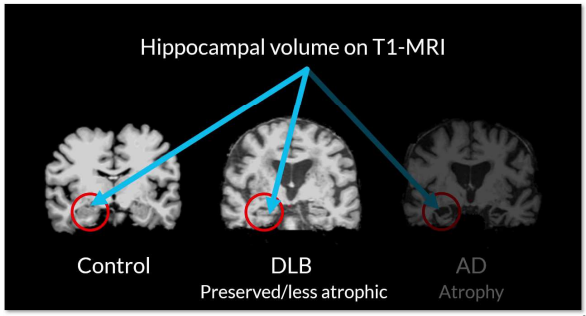
Structural imaging: medial temporal lobe preservation



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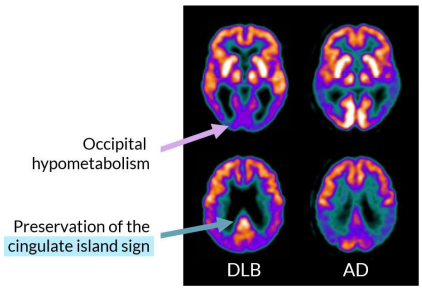
Functional imaging (SPECT/PET)

Functional imaging (SPECT/PET) showing posterior/occipital hypoperfusion/hypometabolism with cingulate sparing



^{18}F-FDG PET imaging

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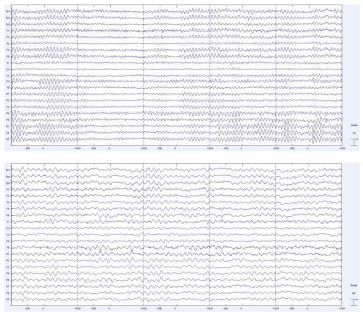
EEG as a biomarker

Prominent posterior slow-wave EEG activity with periodic fluctuations in the pre-alpha/theta range



Examples of 10–20 EEG recordings

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Problems in diagnosing dementia with Lewy bodies

- Insufficient neuropsychological evaluation
  - DLB patients may have more obvious visual-spatial difficulties

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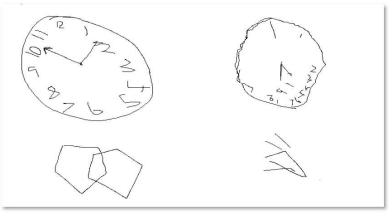
Problems in diagnosing dementia with Lewy bodies

- Insufficient neuropsychological evaluation



MMSE 18/30	MMSE 20/30
Orientation 5/10	Orientation 8/10
Short term memory 0/3	Short term memory 2/3

Problems in diagnosing dementia with Lewy bodies

- Insufficient neuropsychological evaluation
- Atypical presentations are common
- Underuse of the "possible" DLB diagnosis
- Difficulty recognising/defining "fluctuation"
- Confidence in assessing motor symptoms
- Failure to ask about core and supportive clinical features
  - Autonomic dysfunction
  - Anosmia
  - REM sleep behaviour disorder
- Impact of Alzheimer co-pathology

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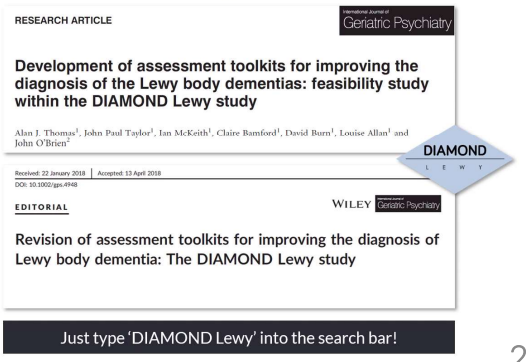
The DIAMOND Lewy study



RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Development of assessment toolkits for improving the diagnosis of the Lewy body dementias: feasibility study within the DIAMOND Lewy study

Alan J. Thomas[1], John Paul Taylor[1], Ian McKeith[1], Claire Bamford[1], David Burn[1], Louise Allan[1] and John O'Brien[2]

DIAMOND L E W Y

Received: 22 January 2018 | Accepted: 13 April 2018

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EDITORIAL

WILEY International Journal of Geriatric Psychiatry

Revision of assessment toolkits for improving the diagnosis of Lewy body dementia: The DIAMOND Lewy study

Just type 'DIAMOND Lewy' into the search bar!

Thomas A.J., *et al., Int J Geriatr Psychiatry*. 2018; **33**(10): 1293-1304

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Diagnostic assessment toolkit for dementia with Lewy bodies

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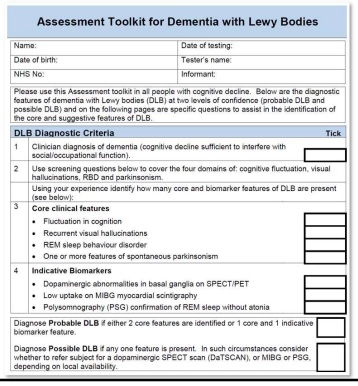


Assessment Toolkit for Dementia with Lewy Bodies

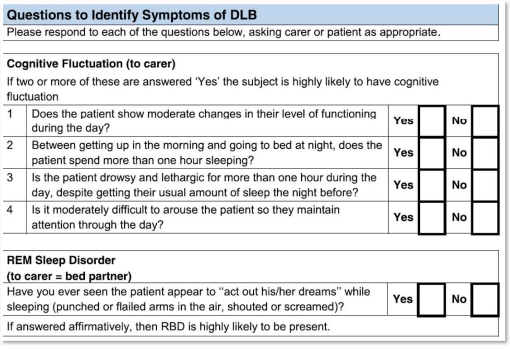
Name:	Date of testing:
Date of birth:	Tester's name:
NHS No:	Informant:

Please use this Assessment toolkit in all people with cognitive decline. Below are the diagnostic features of dementia with Lewy bodies (DLB) at two levels of confidence (probable DLB and possible DLB) and on the following pages are specific questions to assist in the identification of the core and suggestive features of DLB.

	DLB Diagnostic Criteria	Tick
1	Clinician diagnosis of dementia (cognitive decline sufficient to interfere with social/occupational function).	
2	Use screening questions below to cover the four domains of: cognitive fluctuation, visual hallucinations, RBD and parkinsonism.	
	Using your experience identify how many core and biomarker features of DLB are present (see below):	
3	**Core clinical features** • Fluctuation in cognition • Recurrent visual hallucinations • REM sleep behaviour disorder • One or more features of spontaneous parkinsonism	
4	**Indicative Biomarkers** • Dopaminergic abnormalities in basal ganglia on SPECT/PET • Low uptake on MIBG myocardial scintigraphy • Polysomnography (PSG) confirmation of REM sleep without atonia	
	Diagnose **Probable DLB** if either 2 core features are identified or 1 core and 1 indicative biomarker feature.	
	Diagnose **Possible DLB** if any one feature is present. In such circumstances consider whether to refer subject for a dopaminergic SPECT scan (DaTSCAN), or MIBG or PSG, depending on local availability.	

DIAMOND

Diagnostic assessment toolkit for dementia with Lewy bodies



Questions to Identify Symptoms of DLB

Please respond to each of the questions below, asking carer or patient as appropriate.

Cognitive Fluctuation (to carer)

If two or more of these are answered 'Yes' the subject is highly likely to have cognitive fluctuation

1	Does the patient show moderate changes in their level of functioning during the day?	Yes ☐	No ☐
2	Between getting up in the morning and going to bed at night, does the patient spend more than one hour sleeping?	Yes ☐	No ☐
3	Is the patient drowsy and lethargic for more than one hour during the day, despite getting their usual amount of sleep the night before?	Yes ☐	No ☐
4	Is it moderately difficult to arouse the patient so they maintain attention through the day?	Yes ☐	No ☐

REM Sleep Disorder
(to carer = bed partner)

Have you ever seen the patient appear to "act out his/her dreams" while sleeping (punched or flailed arms in the air, shouted or screamed)?	Yes ☐	No ☐

If answered affirmatively, then RBD is highly likely to be present.

DIAMOND

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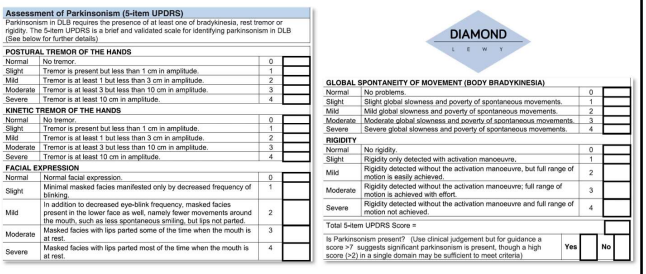
Diagnostic assessment toolkit for dementia with Lewy bodies



Assessment of Parkinsonism (5-item UPDRS)

Parkinsonism in DLB requires the presence of at least one of bradykinesia, rest tremor or rigidity. The 5-item UPDRS is a brief and validated scale for identifying parkinsonism in DLB (See below for further details)

POSTURAL TREMOR OF THE HANDS		
Normal	No tremor.	0
Slight	Tremor is present but less than 1 cm in amplitude.	1
Mild	Tremor is at least 1 but less than 3 cm in amplitude.	2
Moderate	Tremor is at least 3 but less than 10 cm in amplitude.	3
Severe	Tremor is at least 10 cm in amplitude.	4
KINETIC TREMOR OF THE HANDS		
Normal	No tremor.	0
Slight	Tremor is present but less than 1 cm in amplitude.	1
Mild	Tremor is at least 1 but less than 3 cm in amplitude.	2
Moderate	Tremor is at least 3 but less than 10 cm in amplitude.	3
Severe	Tremor is at least 10 cm in amplitude.	4
FACIAL EXPRESSION		
Normal	Normal facial expression.	0
Slight	Minimal masked facies manifested only by decreased frequency of blinking.	1
Mild	In addition to decreased eye-blink frequency, masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted.	2
Moderate	Masked facies with lips parted some of the time when the mouth is at rest.	3
Severe	Masked facies with lips parted most of the time when the mouth is at rest.	4

DIAMOND

GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA)		
Normal	No problems.	0
Slight	Slight global slowness and poverty of spontaneous movements.	1
Mild	Mild global slowness and poverty of spontaneous movements.	2
Moderate	Moderate global slowness and poverty of spontaneous movements.	3
Severe	Severe global slowness and poverty of spontaneous movements.	4
RIGIDITY		
Normal	No rigidity.	0
Slight	Rigidity only detected with activation manoeuvre.	1
Mild	Rigidity detected without the activation manoeuvre, but full range of motion is easily achieved.	2
Moderate	Rigidity detected without the activation manoeuvre; full range of motion is achieved with effort.	3
Severe	Rigidity detected without the activation manoeuvre and full range of motion not achieved.	4
Total 5-item UPDRS Score =		
Is Parkinsonism present? (Use clinical judgement but for guidance a score >7 suggests significant parkinsonism is present, though a high score (>2) in a single domain may be sufficient to meet criteria)		Yes / No

Toolkit videos are available on the DIAMOND Lewy website as well as on YouTube

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Impact of the diagnostic assessment toolkit

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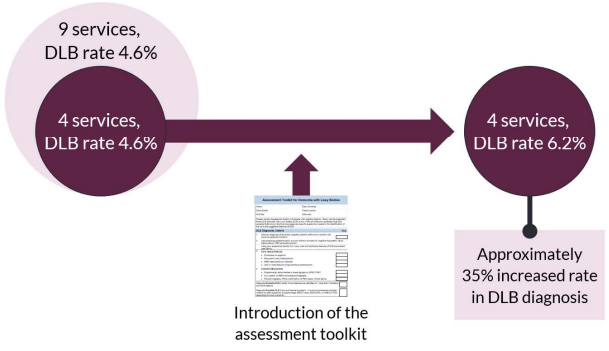
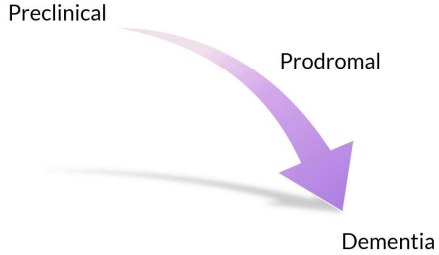


Kane J.P.M. *et al.*, Clinical prevalence of Lewy body dementia. *Alzheimers Res Ther.* 2018; **10**(1): 19
Surendranathan A., Kane J., Bentley A. *et al.*, *Alz Res Therapy*, 2021; **13**: 50

Emerging concepts



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Emerging concepts

VIEWS & REVIEWS | OPEN ACCESS

Research criteria for the diagnosis of prodromal dementia with Lewy bodies

Ian G. McKeith, F Med Sci, MD, Tanis J. Ferman, PhD, Alan J. Thomas, PhD, Frédéric Blanc, MD, Bradley F. Boeve, MD, Hiroshige Fujishiro, MD, Kejal Kantarci, MD, MS, Cristina Muscio, PhD, John T. O'Brien, F Med Sci, DM, Ronald B. Postuma, MD, MSc, Dag Aarsland, PhD, Clive Ballard, MD, Laura Bonanni, MD, PhD, Paul Donaghy, PhD, Murat Emre, MD, James E. Galvin, MD, MPH, Douglas Galasko, MD, Jennifer G. Goldman, MD, MS, Stephen N. Gomperts, MD, PhD, Lawrence S. Honig, MD, PhD, Manabu Ikeda, MD, PhD, James B. Leverenz, MD, Simon J.G. Lewis, MD, Karen S. Marder, MD, MPH, Mario Masellis, MD, PhD, David P. Salmon, PhD, John Paul Taylor, MB, BS, PhD, Debby W. Tsuang, MD, Zuzana Walker, MD, and Pietro Tiraboschi, MD, for the prodromal DLB Diagnostic Study Group

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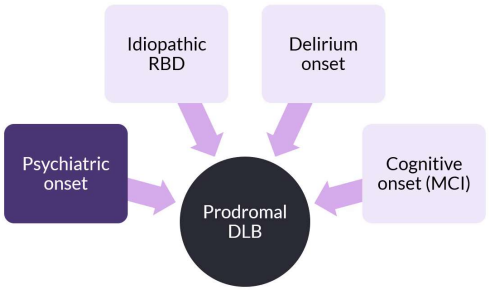
Neurology® 2020;94:743-755. doi:10.1212/WNL.0000000000009323

Emerging concepts



Emerging concepts

- **Diagnosis of MCI-Lewy body**
  - Concern by the patient, informant, or clinician regarding cognitive decline
  - Objective evidence of impairment in 1 or more cognitive domains
  - Preserved or minimally affected performance of previously attained independence in functional abilities, which do not meet the criteria for dementia
- **Core clinical features**
  - Fluctuating cognition
  - Recurrent visual hallucinations
  - REM sleep behaviour
  - Features of parkinsonism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Research criteria for the diagnosis of prodromal dementia with Lewy bodies

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McKeith I.G., et al., *Neurology*. 2020; **94** (17): 743-755

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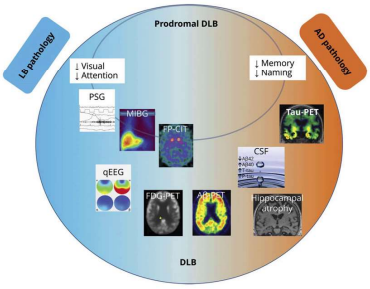
Emerging concepts

Figure Multimodal biomarkers for prodromal DLB



McKeith I.G., et al., *Neurology*. 2020; 94 (17): 743-755

Emerging concepts

The diagnostic criteria remain research based, rather than practical

McKeith I.G., et al., *Neurology*. 2020; 94 (17): 743-755

Management of dementia with Lewy bodies

A complex multisystem disease

27

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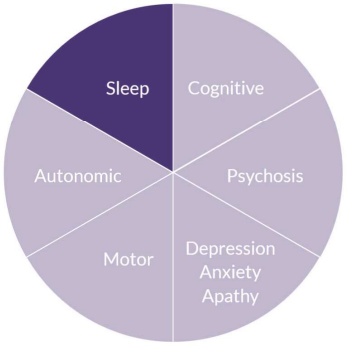
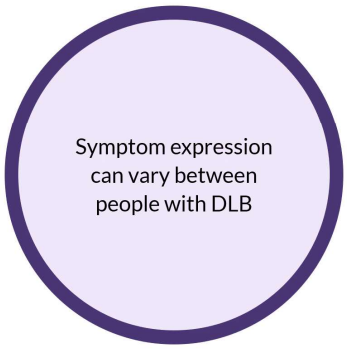
Management of dementia with Lewy bodies



Management of dementia with Lewy bodies



Management of dementia with Lewy bodies

- Multidisciplinary team approach
  - Movement disorder specialists
  - Psychiatrists
  - Neurologists
  - Geriatricians
  - Occupational therapists, speech and language therapists, physiotherapists

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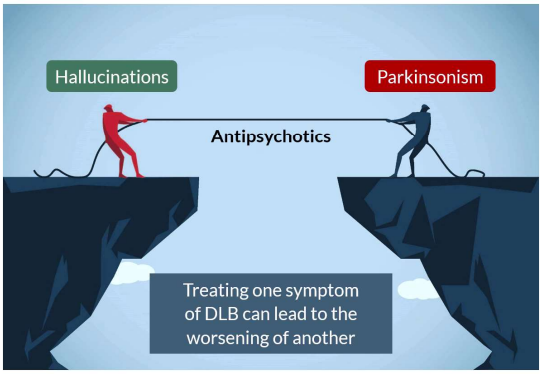
Management of dementia with Lewy bodies

- Multidisciplinary team approach
- Accurate diagnosis
- Identify symptoms that need treatment
- Education and engagement
- Support care providers

DLB therapeutic challenges



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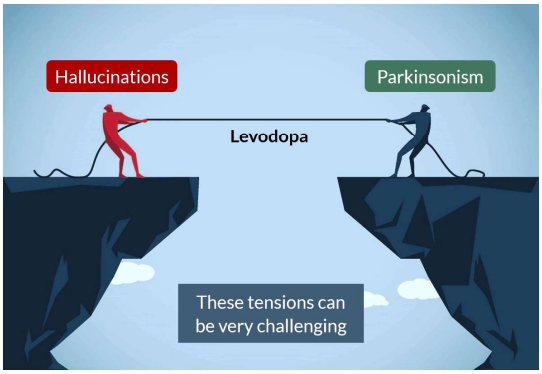
DLB therapeutic challenges



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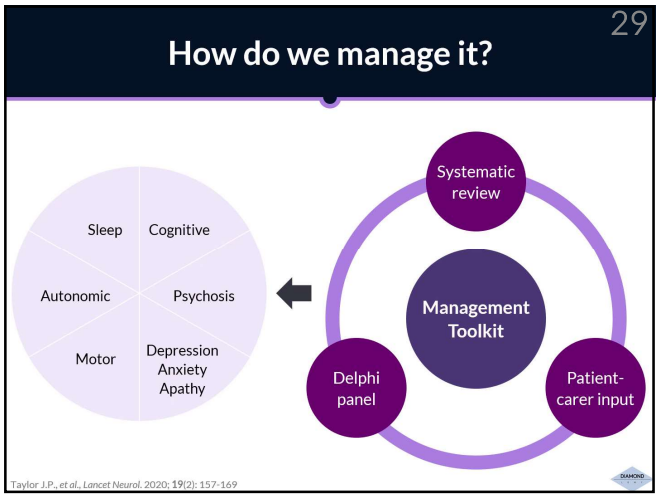

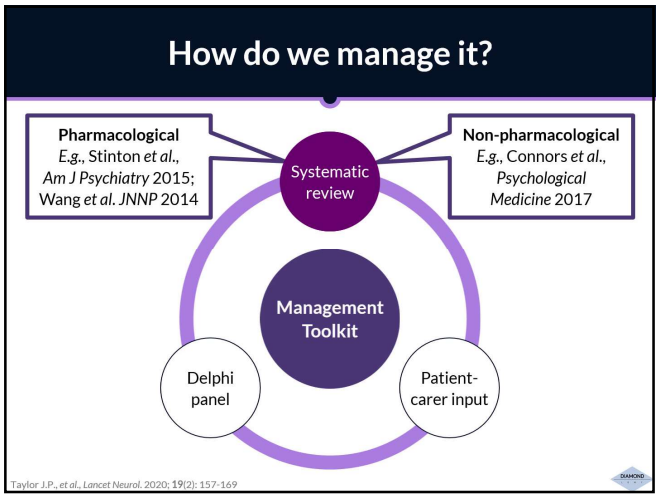

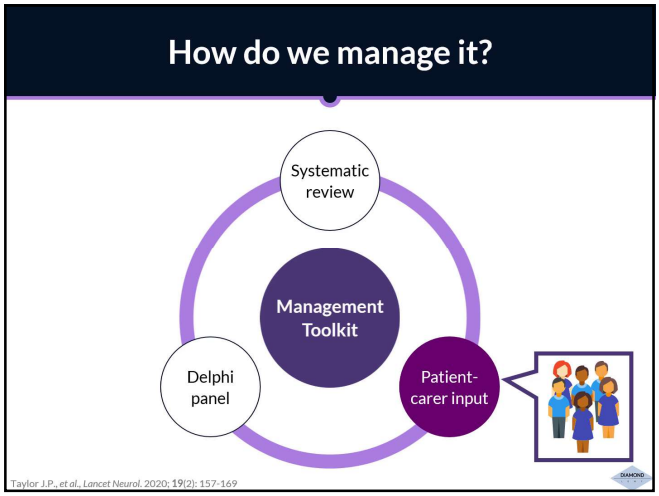

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HSTalks

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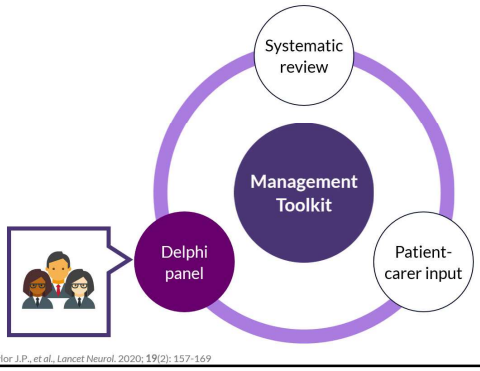
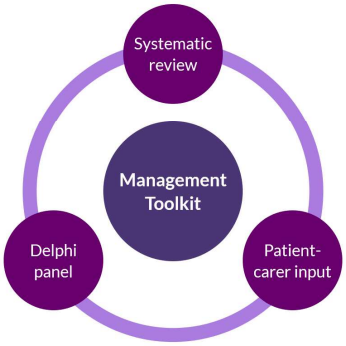
How do we manage it?



Taylor J.P., *et al.*, *Lancet Neurol.* 2020; 19(2): 157-169

Taking a holistic perspective



For further information, see the tab of external links

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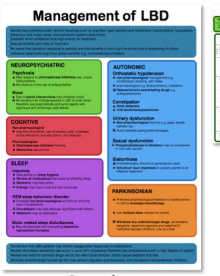
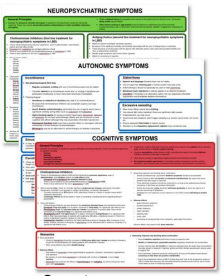
Taking a holistic perspective

DIAMOND

Management toolkit



Overview



Symptom summary

LBD Management Guideline

Reference guidelines

For further information, see the tab of external links

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LBD management guideline

LBD
Management
Guideline

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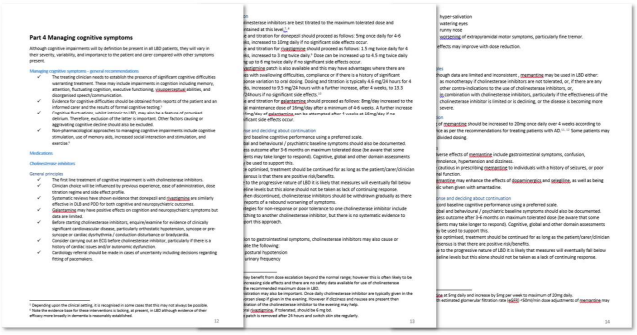
LBD management guideline



Part 4 Managing cognitive symptoms

Although cognitive impairments will by definition be present in all LBD patients, they will vary in their severity, variability, and importance to the patient and carer compared with other symptoms present.

Managing cognitive symptoms: general considerations

- ✓ Establish the presence of significant cognitive difficulties warranting treatment. These may include impairments in cognition including memory, attention, fluctuating cognition, executive functioning, visuoperceptual abilities, and disorganised speech/communication.
- ✓ Evidence for cognitive difficulties should be obtained from reports of the patient and an informed carer and the results of formal cognitive testing.[1]
- ✓ Cognitive fluctuations, whilst intrinsic to LBD, may also be a feature of [illegible]. 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.[2]

Medications

Cholinesterase inhibitors

General principles

- ✓ The first line treatment of cognitive impairment is with cholinesterase inhibitors.
- ✓ Clinician choice will be influenced by previous experience, ease of administration, dose titration regime and side effect profile.
- ✓ Systematic reviews have shown evidence that donepezil and rivastigmine are similarly effective in DLB and PDD for both cognitive and neuropsychiatric outcomes.
- ✓ Galantamine may have positive effects on cognition and neuropsychiatric symptoms but less evidence.
- ✓ Before starting cholinesterase inhibitors, enquire/examine for evidence of clinically significant cardiovascular disease, particularly orthostatic hypotension, syncope or pre-syncope or cardiac dysrhythmia / conduction disturbance or bradycardia.
- ✓ Consider carrying out an ECG before cholinesterase inhibitor, 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.

[1] Depending upon the clinical setting, it is recognised in some cases that this may not always be possible.
[2] Note the evidence base for these interventions is lacking, at present, in LBD although evidence of their efficacy more broadly in dementia is reasonably established.

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[illegible] cholinesterase inhibitors are best titrated to the maximum tolerated dose and maintained at this level.[1]

[illegible] and titration for donepezil should proceed as follows: 5mg once daily for 4-6 [illegible], increased to 10mg daily if no significant side effects occur.

[illegible] 1.5 mg twice daily for 4 weeks, increased to 3 mg twice daily as follows: 1.5 mg twice daily for 4 [illegible], increased to 3 mg twice daily.[1] Dose can be increased up to 4.5 mg twice daily [illegible] up to 6 mg twice daily if no significant side effects occur.

[illegible] patch is also available and this may have advantages where there are [illegible] with swallowing difficulties, compliance or if there is a history of significant [illegible] dose variation to oral dosing. Dosing and titration is typically 4.6 mg/24 hours for 4 [illegible], increased to 9.5 mg/24 hours with a further increase, after 4 weeks, to 13.3 [illegible]hours if no significant side effects.[1]

[illegible] and titration for galantamine should proceed as follows: 8mg/day increased to the [illegible] maintenance dose of 16mg/day after a minimum of 4-6 weeks. A further increase [illegible]mg/day of galantamine can be attempted after 4 weeks at 16mg/day if no [illegible]dicant side effects occur.

[illegible] and deciding about continuation

[illegible] and baseline cognitive performance using a preferred scale.

[illegible] and behavioural / psychiatric baseline symptoms should also be documented.

[illegible]s outcome after 3-6 months on maximum tolerated dose (be aware that some [illegible]ients may take longer to respond). Cognitive, global and other domain assessments [illegible] be used to support this.

[illegible] optimised, treatment should be continued for as long as the patient/carer/clinician [illegible]nsensus is that there are positive risk/benefits.

[illegible] to the progressive nature of LBD it is likely that measures will eventually fail below [illegible] levels but this alone should not be taken as lack of continuing response.

[illegible] discontinued, cholinesterase inhibitors should be withdrawn gradually as there [illegible] are reports of a rebound worsening of symptoms.

[illegible]egies for non-response or poor tolerance to one cholinesterase inhibitor include [illegible]ching to another cholinesterase inhibitor, but there is no systematic evidence to [illegible]ort this approach.

[illegible]n to gastrointestinal symptoms, cholinesterase inhibitors may also cause or [illegible]se the following:

[illegible]postural hypotension

[illegible]rinary frequency

[illegible]

[illegible]s benefit from dose escalation beyond the normal range; however this is often likely to be [illegible]creasing side effects and there are no safety data available for use of cholinesterase [illegible]itors above the licensed dose range.[2]

[illegible]ination may also be important. Once daily cholinesterase inhibitor are typically given in the [illegible]rown sleep if given in the evening. However if dizziness and nausea are present then [illegible]ation of the cholinesterase inhibitor to the evening may help.

[illegible] [illegible]rivastigmine. If tolerated, should be 6 mg bd.

[illegible]patch is removed after 24 hours and a switch skin site regularly.

13

hyper-salivation
watering eyes
runny nose
[illegible]ppearance of extrapyramidal motor symptoms, particularly fine tremor.
[illegible]effects may improve with dose reduction.

[illegible]

[illegible]hough data are limited and inconsistent, memantine may be used in LBD either:
[illegible]as monotherapy if cholinesterase inhibitors are not tolerated, or, if there are any [illegible] other contra-indications to the use of cholinesterase inhibitors; or,
[illegible] in combination with cholinesterase inhibitors, particularly if the effectiveness of the [illegible] cholinesterase inhibitor is limited or is declining, or the disease is becoming more [illegible] severe.

[illegible]

[illegible] of memantine should be increased to 20mg once daily over 4 weeks according to [illegible]ce as per the recommendations for treating patients with AD.[1,2,3] Some patients may [illegible] divided dosing.

[illegible]

[illegible]erse effects of memantine include gastrointestinal symptoms, confusion, [illegible]ziness, hypertension and dizziness.

[illegible]ution in prescribing memantine to individuals with a history of seizures, or poor [illegible]al function.

[illegible]antadine may enhance the effects of dopaminergics and ketamine, as well as being [illegible]ic when given with amantadine.

[illegible]

[illegible]sing and deciding about continuation

[illegible]ased baseline cognitive performance using a preferred scale.

[illegible]al and behavioural / psychiatric baseline symptoms should also be documented.

[illegible]us outcome after 3-6 months on maximum tolerated dose (be aware that some [illegible]ients may take longer to respond). Cognitive, global and other domain assessments [illegible] be used to support this.

[illegible]e optimised, treatment should be continued for as long as the patient/carer/clinician [illegible]nsensus is that there are positive risk/benefits.

[illegible]e to the progressive nature of LBD it is likely that measures will eventually fail below [illegible]seline levels but this alone should not be taken as a lack of continuing response.

[illegible]

[illegible]ose and titrate as follows: 5mg daily and increase by 5mg per week to maximum of 20mg daily.
[illegible]n estimated glomerular filtration rate (eGFR) <30ml/min dose adjustments of memantine may

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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

- 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. For example:
  - **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:** 4.6 mg/24 hours for 4 weeks, increased to 9.5mg/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 (be aware that some patients may take longer to respond). 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**
  - 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.

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Cognitive symptoms

Cholinesterase Inhibitors

- 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. For example:
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  - **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 (be aware that some patients may take longer to respond). 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**
  - 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.

For further information, see the tab of external links

18–month cluster design pragmatic trial

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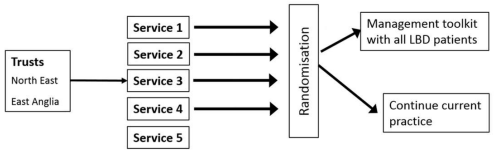
RESEARCH ARTICLE

Introduction of a Management Toolkit for Lewy Body Dementia: A Pilot Cluster-Randomized Trial

John T. O'Brien, DM,[1,2*] Ian G. McKeith, FMedSci,[3] Alan J. Thomas, PhD,[3] Claire Bamford, BA,[4] Luke Vale, PhD,[4] Sarah Hill, PhD,[4] Louise Allan, PhD,[5] Tracy Finch, PhD,[6] Richard McNally, PhD,[7] Louise Hayes, PhD,[7] Ajenthan Surendranathan, PhD,[1] Joseph P.M. Kane, PhD,[1] Sarah Dunn, MSc,[8] Allison Bentley, MSc,[1,2] Sally Barker, BSc,[1] James Mason, PhD,[9] David Burn, MD,[1] and John-Paul Taylor, PhD[2]



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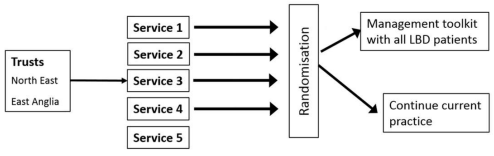
18–month cluster design pragmatic trial

3 sites in the North East

4 sites in East Anglia

Carers reported less marked patient deterioration on the global outcome measure (p<0.05)

Carers have reduced burden (p<0.01) and depression (p<0.05)



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Pathways going forward for treatment of DLB

- Potential disease modifying therapies
- Targeting early-stage disease
  - *E.g.*, Lewy body MCI, RBD
- Novel approaches, including non-pharmacological
- Repurposing drugs from other diseases

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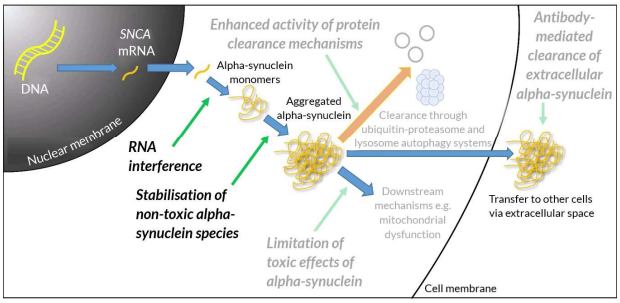
Targeting alpha-synuclein



Alpha-synuclein transcription blockers, *e.g.*, salbutamol, clenbuterol

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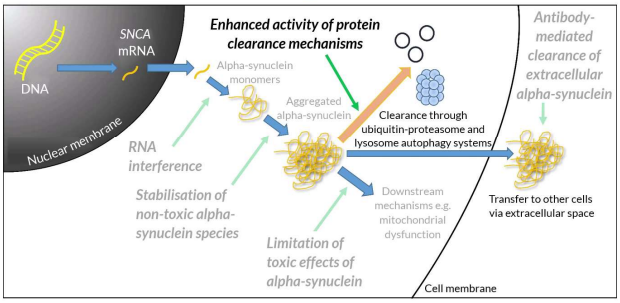
Stoker T.B. *et al. Front Neurosci.* 2018;12:493

Targeting alpha-synuclein



Autophagy enhancers
e.g., Ambroxol, Tyrosine Kinase Inhibitors nilotinib/bosutinib

Stoker T.B. *et al. Front Neurosci.* 2018;12:493

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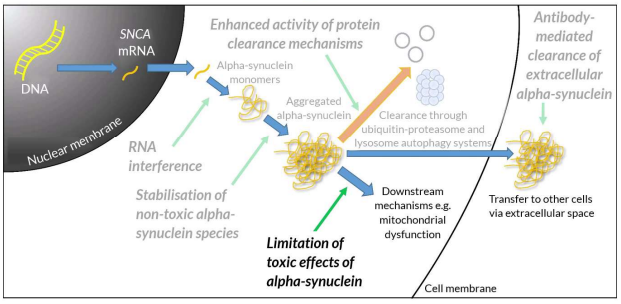
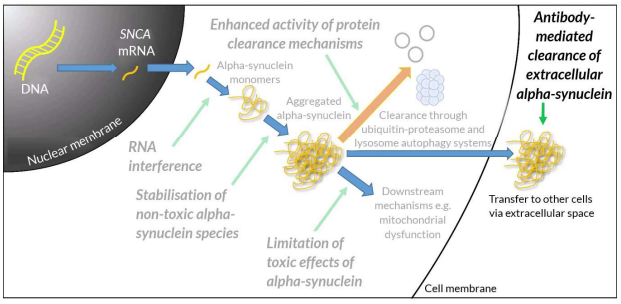
Targeting alpha-synuclein



Selective inhibitors of phosphodiesterase 9
e.g., E2027 Eisai

Stoker T.B. *et al. Front Neurosci.* 2018;12:693

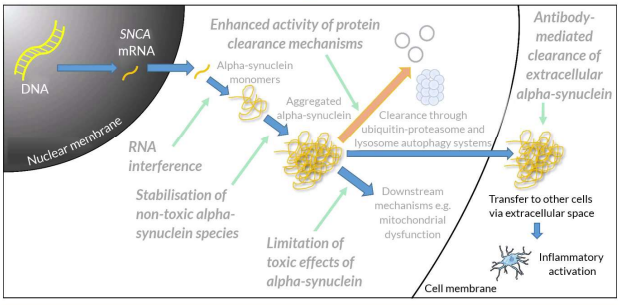
Targeting alpha-synuclein



Immunotherapies

Stoker T.B. *et al. Front Neurosci.* 2018;12:693

Targeting alpha-synuclein



Anti-inflammatory therapies
E.g., NSAIDs/Neflamapimod

Stoker T.B. *et al. Front Neurosci.* 2018;12:693

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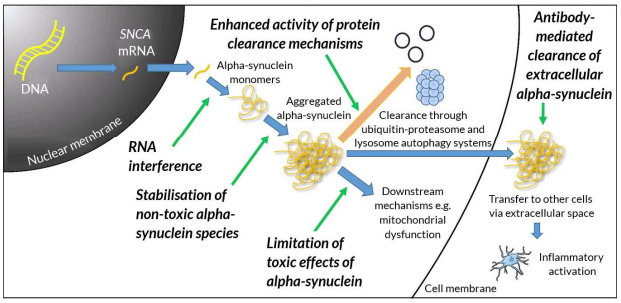
Prof. John-Paul Taylor – Newcastle University, UK

Targeting alpha-synuclein



These areas are currently under investigation, with several different drugs being proposed

Stoker T.B. et al. Front Neurosci. 2018; 12: 493