Lewy body dementia: what’s new

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Why is DLB important?

- DLB causes significantly greater functional disability than Alzheimer’s disease
  (McKeith et al, Am J Ger Psychiat 2006;14.7 582-588)

- Care costs of DLB are twice those for Alzheimer’s disease
  (Boström et al, 2007 Int J Ger Psychiat. 22:713-719)

- Quality of life for people with DLB is significantly worse than for AD with 1 in 4 caregivers rating DLB as worse than death!
  (Boström et al, 2007 Alz Dis Ass Dis 21: 150-154)
Very poor outcomes in DLB

Males: 6.7y; Females 7.0y

DLB survival:
Males: 3.3y; females 4.0y

Price et al, 2017
Mueller et al, 2018

Significantly higher acute hospital resource use in DLB than AD

AD survival:
Males: 6.7y; Females 7.0y

DLB survival:
Males: 3.3y; females 4.0y

Courtesy of John O’Brien
Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

ABSTRACT

The Dementia with Lewy Bodies (DLB) Consortium has refined its recommendations about the clinical and pathologic diagnosis of DLB, updating the previous report, which has been in widespread use for the last decade. The revised DLB consensus criteria now distinguish clearly between clinical features and diagnostic biomarkers, and give guidance about optimal methods to establish and interpret these. Substantial new information has been incorporated about previously reported aspects of DLB, with increased diagnostic weighting given to REM sleep behavior disorder and $^{123}$Iodine-metaiodobenzylguanidine (MIBG) myocardial scintigraphy. The diagnostic role of other neuroimaging, electrophysiologic, and laboratory investigations is also described. Minor modifications to pathologic methods and criteria are recommended to take account of Alzheimer disease neuropathologic change, to add previously omitted Lewy-related pathology categories, and to include assessments for substantia nigra neuronal loss. Recommendations about clinical management are largely based upon expert opinion since randomized controlled trials in DLB are few. Substantial progress has been made since the previous report in the detection and recognition of DLB as a common and important clinical disorder. During that period it has been incorporated into DSM-5, as major neurocognitive disorder with Lewy bodies. There remains a pressing need to understand the underlying neurobiology and pathophysiology of DLB, to develop and deliver clinical trials with both symptomatic and disease-modifying agents, and to help patients and carers worldwide to inform themselves about the disease, its prognosis, best available treatments, ongoing research, and how to get adequate support. Neurology® 2017:89:1-13
### Core clinical features

- Recurrent visual hallucinations that are typically well formed and detailed.
- 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.
- Fluctuating cognition with pronounced variations in attention and alertness.
- REM sleep behaviour disorder, which may precede cognitive decline.

### 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.
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Indicative biomarkers
Dementia: assessment, management and support for people living with dementia and their carers

Further tests for dementia with Lewy bodies

1.2.20 If the diagnosis is uncertain (see recommendation 1.2.14) and dementia with Lewy bodies is suspected, use $^{123}$I-FP-CIT SPECT.

1.2.21 If $^{123}$I-FP-CIT SPECT is unavailable, consider $^{123}$I-MIBG cardiac scintigraphy.

1.2.22 Do not rule out dementia with Lewy bodies based solely on normal results on $^{123}$I-FP-CIT SPECT or $^{123}$I-MIBG cardiac scintigraphy.
• **Probable DLB can be diagnosed if:**
  – Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, **or**
  – 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:**
  – Only one core clinical feature of DLB is present, with no indicative biomarker evidence, **or**
  – One or more indicative biomarkers is present but there are no core clinical features.

• **DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism.**
But there is an ongoing problem in terms of DLB under-diagnosis.
Clinical prevalence of Lewy body dementia


9 memory services in 5 NHS Trusts with >4500 dementia case notes screened

UK 4.6%

North East

East Anglia

Courtesy of John O’Brien
Variation in diagnostic thresholds

• Few “possible” DLB diagnoses

• Cases in East Anglia had significantly more core features (p=0.007), FP-CIT (DaTSCAN) significantly less often used

![Bar chart showing variation in diagnostic thresholds for DLB](https://via.placeholder.com/150)

Below "probable" DLB Threshold
- % within Region: EA = 13%
- % within Region: NE = 22%

Meeting "Probable" DLB Threshold
- % within Region: EA = 30%
- % within Region: NE = 43%

Exceeding Threshold for "Probable" DLB
- % within Region: EA = 57%
- % within Region: NE = 35%

Courtesy of John O’Brien
DIAMOND-Lewy Programme

Improving the DIAgnosis and Management Of Neurodegenerative Dementia of Lewy body type

Northumberland, Tyne and Wear NHS Foundation Trust
Cambridgeshire and Peterborough NHS Foundation Trust

Jan 2014 to March 2019
Revision of assessment toolkits for improving the diagnosis of Lewy body dementia: The DIAMOND Lewy study

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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Does the patient show moderate changes in their level of functioning during the day?</td>
</tr>
<tr>
<td>2</td>
<td>Between getting up in the morning and going to bed at night, does the patient spend more than one hour sleeping?</td>
</tr>
<tr>
<td>3</td>
<td>Is the patient drowsy and lethargic for more than one hour during the day, despite getting their usual amount of sleep the night before?</td>
</tr>
<tr>
<td>4</td>
<td>Is it moderately difficult to arouse the patient so they maintain attention through the day?</td>
</tr>
</tbody>
</table>

**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)?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>No tremor</td>
<td>0</td>
</tr>
<tr>
<td>Slight</td>
<td>Tremor is present but less than 1 cm in amplitude.</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>Tremor is at least 1 but less than 3 cm in amplitude.</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>Tremor is at least 3 but less than 10 cm in amplitude.</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>Tremor is at least 10 cm in amplitude.</td>
<td>4</td>
</tr>
</tbody>
</table>

### KINETIC TREMOR OF THE HANDS

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>No tremor</td>
<td>0</td>
</tr>
<tr>
<td>Slight</td>
<td>Tremor is present but less than 1 cm in amplitude.</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>Tremor is at least 1 but less than 3 cm in amplitude.</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>Tremor is at least 3 but less than 10 cm in amplitude.</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>Tremor is at least 10 cm in amplitude.</td>
<td>4</td>
</tr>
</tbody>
</table>

### FACIAL EXPRESSION

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal facial expression.</td>
<td>0</td>
</tr>
<tr>
<td>Slight</td>
<td>Minimal masked facies manifested only by decreased frequency of blinking.</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>In addition to decreased eye-blink frequency, masked facies present in the lower face as well, namely fewer movements around the mouth.</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>Masked facies at rest.</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Masked facies at rest.</td>
<td></td>
</tr>
</tbody>
</table>

### GLOBAL SPONTANEOUS MOVEMENT

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>No problem</td>
<td>0</td>
</tr>
<tr>
<td>Slight</td>
<td>Slight global rigidity</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Mild global rigidity</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate global rigidity</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Severe global rigidity</td>
<td></td>
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</table>

### RIGIDITY

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>No rigidity</td>
<td>0</td>
</tr>
<tr>
<td>Slight</td>
<td>Rigidity of the extremities</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Rigidity of the extremities</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Rigidity of the extremities</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Rigidity of the extremities</td>
<td></td>
</tr>
</tbody>
</table>

**Total 5-item UPDRS:**

Is Parkinsonism present? (Use clinical judgement but for guidance a score >7 suggests significant Parkinsonism, though a high score (>/2) in a single domain may be sufficient to meet criteria.)

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
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</table>
Revision of assessment toolkits for improving the diagnosis of Lewy body dementia: The DIAMOND Lewy study

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. |
| 3. Using your experience identify how many core and biomarker features of DLB are present (see below): |
| 4. Indicative Biomarkers |
| 4.1 Dopaminergic abnormalities in basal ganglia on SPECT/PET |
| 4.2 Low uptake on MIBG myocardial scintigraphy |
| 4.3 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.

Repeat survey of all consecutive cases after introduction of the diagnostic toolkits

**Improvements in diagnostic rates of DLB by \( \approx 35\% \) (Kane et al. under submission)**

\[ p < 0.05 \]
Dementia with Lewy bodies: a multi-symptom disease
Just published.....

New evidence on the management of Lewy body dementia

DIAMOND-Lewy

Welcome to the NIHR Funded DIAMOND-Lewy website.

On here you can download the Assessment Toolkits, and the Management Toolkit, review our Publications, and look at historical information About the project.
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
  - visuo-perceptual 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.
- Global/behavioural/cognitive baseline symptoms should be documented.
- 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 may be 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.
Cognitive symptoms – key points from guidelines

• First line - cholinesterase inhibitors
• Up to clinician but systematic reviews indicate:
  – Donepezil and rivastigmine are similarly effective in DLB / PDD
  – Galantamine may have positive effects on cognition and neuropsychiatric symptoms but data are limited.
• Rivastigmine patch consider
  – swallowing difficulties
  – compliance issues
  – history of significant response variation to oral dosing
## Assessments of Improvement With Donepezil or Rivastigmine Compared With Placebo (Four Studies, N=916)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Group</th>
<th>Control Group</th>
<th>Risk Ratio(^a) (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td><strong>DLB, donepezil</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mori et al. (15)</td>
<td>18</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>18</td>
<td>10</td>
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</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
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<tr>
<td>Test for overall effect: Z=2.23, p=0.03</td>
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<tr>
<td><strong>PDD, donepezil</strong></td>
<td></td>
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<tr>
<td>Aarsland et al. (16)</td>
<td>5</td>
<td>12</td>
<td>2</td>
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<tr>
<td>Dubois et al. (17)</td>
<td>85</td>
<td>170</td>
<td>68</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>182</td>
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<tr>
<td>Total events</td>
<td>90</td>
<td>70</td>
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<tr>
<td>Heterogeneity: (\chi^2=0.88, df=1, p=0.35; I^2=0%)</td>
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<tr>
<td>Test for overall effect: Z=2.10, p=0.04</td>
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<tr>
<td><strong>PDD, rivastigmine</strong></td>
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<tr>
<td>Emre et al. (22)</td>
<td>134</td>
<td>329</td>
<td>49</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>329</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>134</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
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<td>Test for overall effect: Z=2.31, p=0.02</td>
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<td><strong>Total (95% CI)</strong></td>
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<tr>
<td></td>
<td>539</td>
<td>377</td>
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<tr>
<td>Total events</td>
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<td>129</td>
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<td>Heterogeneity: (\chi^2=2.60, df=3, p=0.46; I^2=0%)</td>
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<td>Test for overall effect: Z=3.61, p=0.0003</td>
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<td></td>
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<tr>
<td>Test for subgroup differences: (\chi^2=1.63, df=2, p=0.44; I^2=0%)</td>
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### Box plot: Clinical Global Impression of Change (CGIC) change from baseline (improvements)
### Box plot: Clinical Global Impression of Change (CGIC) change from baseline (no deterioration)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Group</th>
<th>Control Group</th>
<th>Risk Ratio(a) (95% CI)</th>
<th>Risk Ratio(b) (95% CI)</th>
</tr>
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<tbody>
<tr>
<td><strong>DLB, donepezil</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mori et al. (15)</td>
<td>27 events, 28 total</td>
<td>15 events, 30 total</td>
<td>20.8% 1.93 (1.34, 2.78)</td>
<td>20.8% 1.93 (1.34, 2.78)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
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<tr>
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<tr>
<td>Test for overall effect: Z=3.53, p=0.0004</td>
<td></td>
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<tr>
<td><strong>PDD, donepezil</strong></td>
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</tr>
<tr>
<td>Dubois et al. (17)</td>
<td>128 events, 170 total</td>
<td>117 events, 170 total</td>
<td>40.5% 1.09 (0.96, 1.25)</td>
<td>40.5% 1.09 (0.96, 1.25)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Total events</td>
<td>128</td>
<td>117</td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z=1.33, p=0.18</td>
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<tr>
<td><strong>PDD, rivastigmine</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Emre et al. (22)</td>
<td>218 events, 329 total</td>
<td>95 events, 165 total</td>
<td>38.7% 1.15 (0.99, 1.34)</td>
<td>38.7% 1.15 (0.99, 1.34)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
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<tr>
<td>Total events</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
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<tr>
<td>Total events</td>
<td>527</td>
<td>365</td>
<td>100.0% 1.26 (1.01, 1.57)</td>
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</table>

*\(a\) weighted by study size*  
*\(b\) summary statistic of risk ratios across subgroups*  

Heterogeneity: \(\tau^2=0.03; \chi^2=8.23, \text{df}=2, \text{p}=0.02; \text{I}^2=76\%\)  
Test for overall effect: Z=2.00, p=0.04  
Test for subgroup differences: \(\chi^2=8.21, \text{df}=2, \text{p}=0.02; \text{I}^2=75.6\%\)
### Experimental Group

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<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference* (95% CI)</th>
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<td>Subtotal (95% CI)</td>
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<td>61</td>
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<td>10.7%</td>
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</table>

| Total (95% CI) | 692 | 510 | 100.0% | 1.26 (0.66, 1.86) |  |
| Heterogeneity: tau²=0.27; χ²=12.20, df=7, p=0.09; I²=43%  |     |     |       |        |                           |
| Test for overall effect: Z=4.10, p<0.0001  |     |     |       |        |                           |
| Test for subgroup differences: χ²=3.19, df=3, p=0.36; I²=5.9%  |     |     |       |        |                           |
Cognitive symptoms – key points from guidelines

• **Memantine**
  – Data are limited and inconsistent
  – Use as monotherapy if cholinesterase inhibitors are not tolerated, or, if there are any other contraindications to the use of cholinesterase inhibitors, or,
  – 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.
5mg memantine or placebo

Increased to 10mg bd by week 4

CHEIs allowed

24 weeks treatment

Blinded rater at weeks 0, 12 and 24
Primary Outcome was CGIC – P=0.03 (MWU)

27% improved on drug
0% improved on placebo

More improvement in PDD than DLB?

1.9 point difference in MMSE (greater than CHEIs)

No change in UPDRS or NPI

20% dropouts on drug and 23% placebo – no consistent pattern, no increased confusion on drug.
199 patients with DLB or PDD randomised to memantine 20mg once daily or placebo. Included titration phase.

No CHEIs, no psychotopics initiated during study.

No primary outcome specified

80% completed 24 weeks of treatment

Stroke, falls and worsening dementia were most common SAEs

Dropouts equally common in active (11%) and placebo (12%) groups
Memantine for patients with Parkinson’s disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial

Murat Enre, Magda Tolaki, Ulvaldo Bonuccelli, Alain Destée, Eduardo Tolosa, Alexandra Kutselnigg, Andrés Ceballos-Baumann, Slobodan Zdravkovic, Anna Bladström, Roy Jones, on behalf of the 11018 Study Investigators

Small improvements in CGIC and NPI (delusions, hallucinations, eating and sleeping) in DLB group after 24 weeks but no change in PDD.

Cognitive test scores did not consistently improve in either treatment group, and the groups did not differ significantly in activities of daily living scores, motor symptoms, or caregiver burden.
NIHR-HTA call

Health Technology Assessment Programme

National Institute for Health Research

Australian Government
National Health and Medical Research Council

HTA no 18/189

Combination treatment for dementia with Lewy Bodies and Parkinson's disease dementia
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/24 hours 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 antecedent 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.
Neuropsychiatric symptoms – key points from guidelines

• **First line - cholinesterase inhibitors**
  – Donepezil and rivastigmine
    • RCTs report neuropsychiatric composite score improvements
  – Galantamine
    • preliminary evidence of improved cognitive fluctuations, sleep, and psychiatric symptoms in DLB

• **Second line**
  – Memantine
  – Antipsychotics.....
Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study

Ian McKeith, Teodoro Del Ser, PierFranco Spano, Murat Emre, Keith Wesnes, Ravi Anand, Ana Clicin-Sain, Roberto Ferrara, René Spiegel

N = 120 DLB

30% improvement (Neuropsychiatric inventory) from baseline at wk 20

67% rivastigmine group
30% placebo group
p<=0.03

MMSE treatment vs. control 1.5 points vs. -0.1 points (p=0.07)
Delusions
Hallucinations
Cognitive fluctuations
DLB Challenges in relation to psychosis

Dopaminergic therapies / anticholinergic medications

Need to treat motor symptoms

Need to treat psychotic symptoms

Negative effect on cognition and behavior, leading to confusion and psychosis

Often many “tensions” between treating one symptom and worsening another
DLB and antipsychotics

• Neuroleptic sensitivity
• Increased mortality 2-3x in 50% - no predictors
• Atypicals seem similar to conventional antipsychotics but no RCT evidence!
• No decent trial evidence regarding efficacy
Pimavanserin in Parkinson’s disease psychosis

- Highly selective 5HT2A receptor inverse agonist
  - Improvements in psychosis on Scale for Assessment of Positive Symptoms in Parkinson’s Disease (SAPS-PD) score
  - Improvements in night-time sleep and daytime somnolence
  - Well tolerated and did not worsen motor symptoms
  - Effective across cognitive scores (MMSE < or > 25)

Cummings et al. Lancet 2013
Harmony Phase III clinical trial

- 392 participants who had dementia and recent hallucinations or delusions (also known as dementia-related psychosis).
- Included Alzheimer’s disease, dementia with Lewy bodies, Parkinson’s disease dementia, vascular dementia, and frontotemporal dementia spectrum disorders.
- Outcome was time to relapse:
  - Met the primary endpoint of the study and stopped at the pre-planned interim analysis
  - Reduced relapse of psychosis by 2.8 fold compared to placebo (p=0.0023)
Significant on NPI-psychosis at wk 6 (primary outcome)

Not significant at wk 2, 4, 9, & 12, or on any secondary outcomes

*Figure 2: Adjusted mean change from baseline to week 12 in the NPI-NH psychosis score
Error bars are SE. NPI-NH=Neuropsychiatric Inventory-Nursing Home version.*
The preferred pharmacological treatment of parkinsonism in LBD is levodopa monotherapy.

Use the minimal levodopa dose required for benefit.

Either co-careldopa (carbidopa/levodopa) or co-beneldopa (levodopa/benserazide hydrochloride) may be used.

Start low, and increase dose slowly: typical initiation doses are lower than in Parkinson’s disease (e.g. 50mg (expressed as levodopa) taken 1-3 times daily).

Monitor closely for side effects, including psychosis, postural hypotension, sedation, postural hypotension, nausea and vomiting.

Zonisamide 25mg to 50 mg once a day as an adjunct to levodopa may have some motor benefits in PD and DLB.

Consider speech and language therapy referral for motor related speech and swallowing problems.

Physiotherapy may help with freezing of gait, gait re-education, improvement in balance, power and flexibility, enhanced mobility decrease the risk of falls and improve functional independence.

In LBD cognitive impairment and other comorbid symptoms can diminish engagement with therapy but outcomes may still be positive.

Occupational therapy assessment and home adaptations can help reduce the impact of motor difficulties and reduce falls risk.

Given increased falls risk in LBD vitamin D supplementation should be considered if appropriate.

A gradual and systematic simplification of the antiparkinsonian drug regimen is often necessary to balance neuropsychiatric symptoms vs. motor benefits.

Where anti-parkinsonian drug regimes are being altered, this should be done in close collaboration with the original prescriber of the medicines where possible.

Withdraw (in following order) one at a time:

- anticholinergic drugs
- amantadine
- selegiline
- dopamine agonists and catechol-O-methyltransferase inhibitors.
Effects of Dopaminergic Medications on Psychosis and Motor Function in Dementia with Lewy Bodies
Goldman JG et al Movement Disorders 2008 23:15 2248-2250

• 19 subjects with probable DLB – 74.5yrs; 4.6 yrs duration, MMSE 20.5, 368mg levodopa, 88mg CPZ equivalent, UPDRS III motor 37.6, H&Y 3.3, UPDRS thought disorder 1.55 (mean scores)
• Levodopa increased only (mean 111 mg to 479mg)
• No dopa agonists increased or introduced
• Motor benefit of >10% increase in UPDRS III in one third
• Of these, worsened hallucinations/psychosis in one third
Minimal clinically important change on UPDRS motor score is about 5 points

No worsening of psychiatric symptoms with active treatment

Adverse effects at 50 mg more than 25 mg (somnolence, decreased appetite possibly)

MMSE total score at Week 12 decreased significantly (−0.8) from baseline in the 50mg group compared to placebo. Need extension trial to confirm...
Autonomic symptoms in DLB

- Constipation
- Orthostatic hypotension
- Autonomic symptoms
- Urinary symptoms
- Excessive sweating
- Swallowing difficulties / Drooling

DO NOT NEGLECT!
**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 botulinum 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.

- **Treatment of 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.
- Avoid using metoclopramide given its central dopamine antagonist effect.
- Clonidine (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 symptoms

- REM sleep behavior disorder
- Motor related sleep disturbances
- Insomnia
- Sleep symptoms
- Sleep apnoea
- Excessive daytime sleepiness
- Restless legs / periodic limb movements
**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 µg/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**
- Nocturnal 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.
REM sleep behaviour disorder – pharmacological interventions

• Clonazepam 250 mcg – 500 mcg (up to 1000 mcg) per day taken 30 minutes before bedtime.
• Melatonin 3 mg to 12 mg per day taken before bedtime. Relatively benign side effect profile.
• Remember some medications (e.g. antidepressants) can worsen RBD
Management Toolkit for LBD

18 month cluster design pragmatic trial

3 sites North East

4 sites East Anglia

Trusts
North East
East Anglia

Service 1
Service 2
Service 3
Service 4
Service 5

Randomisation

Management toolkit with all LBD patients

Continue current practice

www.research.ncl.ac.uk/diamondlewy/
Management Toolkit for LBD

18 month cluster design pragmatic trial

<table>
<thead>
<tr>
<th></th>
<th>Control (n=52)</th>
<th>Toolkit (n=75)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>77.0 (7.59)</td>
<td>79.3 (6.97)</td>
<td>0.086</td>
</tr>
<tr>
<td>DLB: PDD</td>
<td>60%:40%</td>
<td>61%:39%</td>
<td>0.846</td>
</tr>
<tr>
<td>Male: Female</td>
<td>81%:19%</td>
<td>77%:23%</td>
<td>0.642</td>
</tr>
<tr>
<td>DEMQOL</td>
<td>0.76 (0.13)</td>
<td>0.78 (0.12)</td>
<td>0.229</td>
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<tr>
<td>NPI</td>
<td>25.0 (17.5)</td>
<td>20.0 (18.0)</td>
<td>0.125</td>
</tr>
<tr>
<td>UPDRS</td>
<td>43.7 (19.1)</td>
<td>38.2 (18.6)</td>
<td>0.112</td>
</tr>
<tr>
<td>GDS</td>
<td>5.7 (3.5)</td>
<td>5.6 (3.3)</td>
<td>0.899</td>
</tr>
<tr>
<td>MMSE</td>
<td>20.8 (6.1)</td>
<td>21.4 (6.1)</td>
<td>0.581</td>
</tr>
<tr>
<td>Carer Zarit</td>
<td>27.5 (15.6)</td>
<td>22.6 (15.3)</td>
<td>0.082</td>
</tr>
<tr>
<td>Carer HADS depression</td>
<td>4.6 (3.8)</td>
<td>4.2 (3.5)</td>
<td>0.553</td>
</tr>
</tbody>
</table>

www.research.ncl.ac.uk/diamondlewy/
Patient outcomes: Global outcome (clinician rated CGIC) preventing worsening

![Bar chart showing patient outcomes]

- Very much/ much worse
- Much better/ better/ no change/ slightly worse

Usual care: Blue bar
Toolkit: Red bar

$p = 0.051$
Patient outcomes: Global outcome (carer rated) preventing worsening

<table>
<thead>
<tr>
<th>Outcome Category</th>
<th>Usual Care</th>
<th>Toolkit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very much/ much worse</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Much better/ better/ no change/ slightly worse</td>
<td>60</td>
<td>85</td>
</tr>
</tbody>
</table>

\[p=0.01\]
### Carer outcomes (median regression analysis, adjusting for baseline values and cluster)

<table>
<thead>
<tr>
<th></th>
<th>Usual care</th>
<th>Toolkit</th>
<th>Group difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HADS anxiety: Baseline</strong></td>
<td>6.5</td>
<td>4.0</td>
<td>0.04 (-2.1, 2.2)</td>
<td>0.973</td>
</tr>
<tr>
<td>6 months</td>
<td>6.0</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HADS depression: Baseline</strong></td>
<td>3.0</td>
<td>4.0</td>
<td>-1.2 (-2.8, -0.1)</td>
<td>0.043</td>
</tr>
<tr>
<td>6 months</td>
<td>4.0</td>
<td>3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zarit: Baseline</strong></td>
<td>26.0</td>
<td>22.0</td>
<td>-6.9 (-12.4, -1.4)</td>
<td>0.011</td>
</tr>
<tr>
<td>6 months</td>
<td>29.5</td>
<td>23.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Future
Nilotinib reverses loss of dopamine neurons and improves motor behavior via autophagic degradation of α-synuclein in Parkinson’s disease models

Michaeline L. Hebron†, Irina Lonskaya† and Charbel E.-H. Moussa†

Department of Neuroscience, Laboratory for Dementia and Parkinsonism, Georgetown University Medical Center, Washington, DC 20057, USA

Received March 20, 2013; Revised and Accepted April 22, 2013

Nilotinib - adult anti-leukaemic agent which inhibits tyrosine kinase Ab which is over-expressed in neurodegeneration.

Nilotinib administration enhances autophagic degradation of α-synuclein, protects SN neurones and ameliorates motor symptoms in A53T mice.
Nilotinib Effects in Parkinson’s Disease and Dementia with Lewy Bodies


aDepartment of Neurology, Laboratory for Dementia and Parkinsonism, National Parkinson’s Foundation Center for Excellence, Translational Neurotherapeutics Program, Georgetown University Medical Center, Washington, DC, USA
bDepartment of Neurology, National Parkinson’s Foundation Center for Excellence, Translational Neurotherapeutics Program, Movement Disorders Program, MedStar Georgetown Hospital, Washington, DC, USA
cDepartment of Biostatistics, Georgetown University Medical Center, Washington, DC, USA

Open label study. n=5 on 150 mg and n=7 on 300 mg daily.

Well tolerated

MMSE increase of 3.85 points (150 mg) and 3.5 (300 mg) points at six months (24-week).

Returned to baseline at the 36-week follow up visit

PD Nilotinib study (Georgetown University)
75 Parkinson disease, doses of 150 or 300 mg

Reasonably tolerated

12 months treatment altered CSF biomarkers, dopamine turnover and oligomeric a-syn + tau.

No significant differences were seen in motor and nonmotor outcomes between the nilotinib groups and the placebo group but study is underpowered

Phase III next step.....
Ambroxol

Enhance function of glucocerebrosidase
Reduce alpha-synuclein in neurons

AIM-PD

- N=17 Parkinson’s patients - 8 with GBA1 mutations and 9 without GBA1 mutations
- Ambroxol crosses the blood-brain barrier
- Increases β-glucocerebrosidase enzyme levels
- Increases cerebrospinal fluid α-synuclein levels
- UPDRS improvements by 6.8 points
Deep brain stimulation of cholinergic nuclei

Angles of 3387 electrode (10.5 mm length) can be adjusted Both coronal and sagittal angles, To cover both Ventro-postero-lateral GPI and Nucleus basalis Meynert

low frequency stimulation to NBM?
Gratwicke et al. Neurosci Biobehav Rev 2013

UCL, London, UK (Foltynie); University Hospital, Rouen, France (Godefroy)
• Surgery and stimulation were well tolerated by all 6 patients
• No consistent improvements in primary cognitive outcomes
• However improvement in scores on the Neuropsychiatric Inventory was observed with NBM DBS compared with sham stimulation (median difference, 5 points)
Drug repurposing exercise

Identification of potential candidate compounds (disease modifying and symptomatic)

Careful systematic review of selected agents for utility in Lewy body dementia

Recommendation for clinical trial development
Quetiapine?

• A number of open-label case series have suggested that quetiapine is effective and relatively safe in DLB patients

• One study suggested:
  – partial or complete amelioration of psychosis in 90% of participants (mean dose 69 mg/day)
  – minimal withdrawal
  – mild worsening of motor symptoms (in 27%)

Takahashi et al. Progress Neuro-Psychopharmacol Biol Psychiatry. 2003
Quetiapine?

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug</th>
<th>No.</th>
<th>Duration (wks)</th>
<th>Primary outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurlan et al.</td>
<td>Quetiapine, average 120 mg daily</td>
<td>23 DLB (+9 PDD and 8 AD)</td>
<td>10</td>
<td>BPRS</td>
<td>No significant effect</td>
</tr>
</tbody>
</table>

• Double blind multi-centre RCT....

Modified from Ballard et al. Drugs Aging. 2013
Aripiprazole?

• Case reports in DLB
  • May improve psychosis, cognition and motor symptoms (single patient study)
  • Improvement in mood symptoms in DLB

– But.....
  • Serious extrapyramidal symptoms have been reported in some...
### Clozapine?

<table>
<thead>
<tr>
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<th>No.</th>
<th>Duration (wks)</th>
<th>Primary outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s Study Group</td>
<td>Clozapine, 6.25 mg daily titrated over at least 10 days to a maximum of 50 mg daily</td>
<td>60 PD (included some PDDs)</td>
<td>64</td>
<td>BPRS, CGIC</td>
<td>Significant improvement compared to placebo group on both BPRS and CGIC</td>
</tr>
<tr>
<td>French Parkinson’s Study Group</td>
<td>Clozapine, 6.25 mg daily titrated over at least 10 days to a maximum of 50 mg daily</td>
<td>60 PD (included some PDDs)</td>
<td>4</td>
<td>PANSS, CGIC</td>
<td>Significant benefit on PANSS positive symptom score and CGIC compared to placebo</td>
</tr>
</tbody>
</table>
DLB and antipsychotics

• **Summary**
  – Quetiapine reasonably well tolerated but unclear efficacy
  – Some evidence for clozapine – but issues of administration and potential side effects etc.

• **Other issues with antipsychotics**
  – Antipsychotics can affect cognition
  – Increase cerebrovascular events and mortality in older people with dementia in general

• **Advice** – use low dose, time delimited, monitored and documented
The problem: DLB under-diagnosis and lack of systematic approach to management

- Clinical DLB diagnostic rates from selected cohorts 4-7% much lower than expected from autopsy studies (Vann-Jones and O’Brien, 2014), but diagnostic rates in routine clinical practice (NHS) unknown

- Previous studies suggest under-recognition and more complex road to diagnosis (Galvin et al, 2010)

Courtesy of John O’Brien

Lowest QoL in LBD
IDEAL study
Wu et al, 2018
Improving management: developing an evidence based management toolkit

- Undertook systematic reviews of pharmacological and non-pharmacological management
- Formed panel of 26 Lewy body dementia experts with broad, including international, representation
- Management statements (n=252) formulated for Lewy body dementia and Delphi process undertaken (3 rounds)
- 161 statements (64%) entered the final toolkit
21 DLB and 30PDD patients completed 24 weeks on 20mg memantine or placebo.

Effects were relatively large (Cohen 0.5-0.8), similar in DLB and PDD and correlated with CGIC improvements.
Open label treatment with memantine from week 26 to month 36

BMJ Open  Treatment effect of memantine on survival in dementia with Lewy bodies and Parkinson's disease with dementia: a prospective study

Kajsa Stubendorff,1,2 Victoria Larsson,1 Clive Ballard,3 Lennart Minthon,1 Dag Aarsland,4,5 Elisabet Londos1

Figure 4  Kaplan-Meier estimates of the rate of survival in
Memantine Case

At 78 years

CT: Normal. MMSE 25/30

After 2 years treatment with rivastigmine alone:
MMSE 21/30, wheelchair, 24h nursing home

After 9 months treatment:
With rivastigmine and memantine
MMSE 26/30

Courtesy of Dr Elisabet Londos
Malmö Skåne University Hospital Sweden
### Core clinical features

- Recurrent visual hallucinations that are typically well formed and detailed.
- 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.
- Fluctuating cognition with pronounced variations in attention and alertness.
- REM sleep behaviour disorder, which may precede cognitive decline.

### 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; 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.

The first three core symptoms typically occur early and may persist throughout the course.
### Core clinical features
- Recurrent visual hallucinations that are typically well formed and detailed.
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- Fluctuating cognition with pronounced variations in attention and alertness.
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### Supportive clinical features
- Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction: constipation, orthostatic hypotension, urinary incontinence; hyperhidrosis; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

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

Now based on movement disorders society criteria.
**Core clinical features**

- Recurrent visual hallucinations that are typically well formed and detailed.
- 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.
- Fluctuating cognition with pronounced variations in attention and alertness.
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- Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

Promotion of RBD to a core symptom
Supportive biomarkers

Prominent posterior slow-wave EEG activity with periodic fluctuations in the pre-alpha/theta range. Evidence is building to support quantitative EEG as a DLB biomarker, characterized by specific abnormalities in posterior derivations. These include a pre-alpha-dominant frequency, either stable or intermixed with alpha/theta/delta activities in pseudoperiodic patterns, which altogether have a predictive value $>90\%$ for the diagnosis of DLB compared with AD. These specific EEG patterns also correlate positively with the severity of clinically observed cognitive fluctuations and may be seen at the MCI stage.
Best Practice Guide for the Treatment of REM Sleep Behaviour Disorder (RBD)

Aurora et al, JOURNAL OF CLINICAL SLEEP MEDICINE (2010) 6 : 1  85-95

• Memantine 10mg bd  (Larsson et al, 2010)

• Clonazepam 0.25mg

• Melatonin 3mg

• Quetiapine 12.5mg

• CHEIs

• L-dopa

• Pramipexole

• Paroxetine

At bedtime
dose titrated
up - all level B

No clear
guidance about
dosing . Can
make RBD
worse
– all level C
Summary

- Diamond Lewy has demonstrated that there is significant variation in the clinical diagnosis of DLB
- Management is also variable
- Assessment toolkits and a management toolkit are freely available
  - Evidence of improvements in diagnosis
  - May be of benefit in management of people with DLB
  - Fit for purpose for NHS use

- PLEASE USE!

https://research.ncl.ac.uk/diamondlewy/
Armodafanil (diphenylmethyl sulfinyl acetamide) is the active R-enantiomer of the racemic drug modafinil.

An analeptic licensed for the treatment of narcolepsy, shift work disorder and excessive daytime sleepiness.

Mode of action uncertain: increases monoamine release and hypothalamic histamine and activates hypothalamic orexin (hypocretin) neurones.
Open label pilot study in n=17 DLB patients
Safety, tolerability, and efficacy of armodafinil therapy for hypersomnia associated with dementia with Lewy bodies

Some improvements in:
NPI (p = 0.003)
Visual hallucinations (p = 0.003)
Agitation (p = 0.02)
Caregiver QOL (p = 0.004)

No adverse events occurred