D.4 Pharmacological management of dementia associated with Parkinson's disease

<table>
<tr><th>Bibliographic reference</th><th>Aarsland,D., Laake,K., Larsen,J.P., Janvin, C., Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study, J Neurol Neurosurg Psychiatry, 72, 708-712, 2002</th></tr>
<tr><td>Study type</td><td>Double-blind randomised controlled trial</td></tr>
<tr><td>Aim of the study</td><td>To assess the safety and efficacy of donepezil in people with PD and cognitive impairment</td></tr>
<tr><td>Country/ies where the study was carried out</td><td>Norway</td></tr>
<tr><td>Study dates</td><td>Not stated, study published in 2002</td></tr>
<tr><td>Source of funding</td><td>Pfizer Norway</td></tr>
<tr><td>Sample size</td><td>N=14 randomised</td></tr>
<tr><td>Inclusion criteria</td><td>People aged 45-95 years with cognitive impairment associated with PD (MMSE score 16 to 26 inclusive) with caregiver support</td></tr>
<tr><td>Exclusion criteria</td><td>Brain disease other than PD, severe medical disorders, concomitant anticholinergics or psychotropic drugs with anticholinergic effects</td></tr>
<tr><td>Details</td><td>20-week double blind, placebo-controlled crossover RCT. Participants were randomised to either donepezil or placebo for 10 weeks, followed by crossover treatment for a further 10 weeks. There was no wash-out period.</td></tr>
<tr><td>Intervention(s)</td><td>Donepezil 5mg daily, increased to 10mg daily after 6 weeks if well tolerated</td></tr>
<tr><td>Comparator(s)</td><td>Placebo</td></tr>
<tr><td>Results</td><td>Efficacy results after 10 weeks treatment:
<table>
<tr><th>Outcome</th><th>Donepezil (n=12)</th><th>Placebo (n=12)</th></tr>
<tr><td>MMSE</td><td>22.8 (3.7)*</td><td>21.0 (5.0)</td></tr>
<tr><td>CIBIC+</td><td>3.3 (0.9)*</td><td>4.1 (0.8)</td></tr>
<tr><td>NPI</td><td colspan="2">Results not presented (no significant difference)</td></tr>
<tr><td>UPDRS III</td><td>31.8 (15.4)</td><td>35.1 (8.1)</td></tr>
<tr><td colspan="3">Values are mean (SD). * P<0.05 compared with placebo</td></tr>
</table>

Adverse events
2 people receiving donepezil withdrew due to adverse events, 0 people withdrew due to adverse events on placebo
Number of adverse events (any) was 12 (SD 11) for donepezil and 9 (SD 7) for placebo</td></tr>
</table>

Bibliographic reference	**Aarsland,D., Laake,K., Larsen,J.P., Janvin, C., Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study, J Neurol Neurosurg Psychiatry, 72, 708-712, 2002**
	Number of adverse events per person, mean (SD) 4.2 (3.2) for donepezil and 2.8 (1.0) for placebo
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? YES 3. Were the groups comparable at baseline for all major confounding/prognostic factors? UNCLEAR 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? NO 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	Included in NICE CG35

Bibliographic reference	**Aarsland,D., Ballard,C., Walker,Z., Bostrom,F., Alves,G., Kossakowski,K., Leroi,I., Pozo-Rodriguez,F., Minthon,L., Londos,E., 20090814, Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial, Lancet Neurology, 8, 613-618, 2009**
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the safety and efficacy of memantine in people with PDD and DLB
Country/ies where the study was carried out	Norway, Sweden and UK
Study dates	2005-2008, study published 2009
Source of funding	The Western Norway Regional Health Authority and Lundbeck
Sample size	N=72 randomised

Bibliographic reference	**Aarsland,D., Ballard,C., Walker,Z., Bostrom,F., Alves,G., Kossakowski,K., Leroi,I., Pozo-Rodriguez,F., Minthon,L., Londos,E., 20090814, Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial, Lancet Neurology, 8, 613-618, 2009**
Inclusion criteria	People with PDD or DLB (MMSE score 12 or above). 47% of people in the memantine group and 63% of people in the placebo group were taking a cholinesterase inhibitor at baseline.
Exclusion criteria	Other brain disease, recent major changes in health status, major depression, moderate to severe renal impairment, heart disease, pulmonary disease, hepatic impairment, abnormal laboratory results, allergy to memantine
Details	Parallel group, 24-week double-blind, placebo-controlled RCT
Intervention(s)	Memantine 5mg daily, increasing to a maintenance dose of 10mg twice daily
Comparator(s)	Placebo
Results	Efficacy results at week 24

	n	Baseline	24 weeks (LOCF)	Change at 24 weeks	Between-group difference
Primary outcome					
CGIC score					
Memantine	30	—	3·5 (1.5)	—	
Placebo	33	—	4·2 (1.5)	—	0·7 (0·04 to 1·39)†
Secondary outcomes					
MMSE					
Memantine	30	20·1 (3·7)	21·5 (4·2)	–1·4 (3·2)‡	
Placebo	33	20·6 (4·2)	20·0 (6·2)	0·5 (4·2)	1·9 (0·06 to 3·8)
NPI					
Memantine	29	15·2 (14·2)	13·7 (12·8)	1·5 (10·8)	
Placebo	33	13·0 (9·9)	11·6 (11·7)	1·4 (10·6)	–0·1 (-1·2 to 4·3)
DAD					
Memantine	30	21·6 (10·8)	20·6 (12·6)	1·0 (6·4)	
Placebo	33	23·8 (8·2)	21·2 (9·5)	2·5 (4·6)§	1·5 (-1·2 to 4·3)
Modified UPDRS III					
Memantine	28	11·1 (5·7)	11·3 (6·1)	0·3(3·1)	
Placebo	30	11·6 (4·1)	11·6 (4·6)	0·0 (4·3)	–0·3 (-2·4 to 1·8)

Bibliographic reference	**Aarsland,D., Ballard,C., Walker,Z., Bostrom,F., Alves,G., Kossakowski,K., Leroi,I., Pozo-Rodriguez,F., Minthon,L., Londos,E., 20090814, Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial, Lancet Neurology, 8, 613-618, 2009**
	Numbers are mean (SD), mean (95% CI), or mean seconds taken to complete the test (SD) *Mann–Whitney test †P=0.03; ‡Wilcoxon Z test P=0.02; §Wilcoxon Z test P=0·004; ¶P=0.045
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? YES 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	None

Bibliographic reference	**Dubois,B., Tolosa,E., Katzenschlager,R., Emre,M., Lees,A.J., Schumann,G., Pourcher,E., Gray,J., Thomas,G., Swartz,J., Hsu,T., Moline,M.L., 20130214, Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study, Movement Disorders, 27, 1230-1238, 2012**
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the efficacy and safety of donepezil in people with PDD
Country/ies where the study was carried out	Multicentre (UK, Germany, Austria, Spain, Russia, France, Australia, New Zealand, South Africa, Canada, Italy, Belgium, Portugal)
Study dates	2002-2005, study published 2012
Source of funding	Eisai
Sample size	N=550 randomised

<table>
<tr><th>Bibliographic reference</th><th>Dubois,B., Tolosa,E., Katzenschlager,R., Emre,M., Lees,A.J., Schumann,G., Pourcher,E., Gray,J., Thomas,G., Swartz,J., Hsu,T., Moline,M.L., 20130214, Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study, Movement Disorders, 27, 1230-1238, 2012</th></tr>
<tr><td>Inclusion criteria</td><td>People aged 40 years and older with PDD (MMSE score 10 to 26 inclusive) with a reliable caregiver</td></tr>
<tr><td>Exclusion criteria</td><td>Other causes of dementia (including DLB), recurrent major depression, previous treatment with cholinesterase inhibitor, allergy to donepezil, concomitant anticholinergics</td></tr>
<tr><td>Details</td><td>Parallel group, 24-week double-blind, placebo-controlled RCT</td></tr>
<tr><td>Intervention(s)</td><td>Donepezil 5mg or 10mg daily</td></tr>
<tr><td>Comparator(s)</td><td>Placebo</td></tr>
<tr><td>Results</td><td>Efficacy results at week 24 (LOCF)
<table>
<tr><th></th><th>Donepezil 5mg vs placebo</th><th>Donepezil 10mg vs placebo</th></tr>
<tr><td colspan="3">Co-primary outcomes</td></tr>
<tr><td>ADAS-cog</td><td>MD –1.45, 95%CI –2.9 to 0.00, P=0.05</td><td>MD –1.45, 95%CI –3.04 to 0.15, P=0.076</td></tr>
<tr><td>CIBIC+ overall change score</td><td>3.7 (SD 1.12) vs. 3.9 (SD 1.27), P=0.113</td><td>3.6 (SD 1.29) vs. 3.9 (SD 1.27), P=0.04</td></tr>
<tr><td colspan="3">Secondary outcomes</td></tr>
<tr><td>MMSE</td><td>MD 1.44, 95%CI 0.81 to 2.07, P<0.001</td><td>MD 1.66, 95%CI 1.02 to 2.29, P<0.001</td></tr>
<tr><td>D-KEFS:
Letter fluency
Category fluency
Category switching</td><td>
MD 2.56, 95%CI 0.99 to 4.14, P=0.001
MD 3.67, 95%CI 2.26 to 5.09, P<0.001
MD 1.14, 95%CI 0.46 to 1.82, P=0.001</td><td>
MD 3.12, 95%CI 1.52 to 4.72, P<0.001
MD 4.22, 95%CI 2.78 to 5.65, P=0.001
MD 1.21, 95%CI 0.52 to 1.90, P<0.001</td></tr>
<tr><td>BTA</td><td>MD 0.78, 95%CI 0.22 to 1.34, P=0.007</td><td>MD 1.00, 95%CI 0.42 to 1.57, P<0.001</td></tr>
<tr><td>DAD</td><td>MD 2.27, 95%CI –0.74 to 5.28, P=0.138</td><td>MD 2.24, 95%CI –0.82 to 5.30, P=0.15</td></tr>
<tr><td>SE scale</td><td>MD –0.68, 95%CI –3.19 to 1.84, P=0.598</td><td>MD –0.33, 95%CI –2.90 to 2.23, P=0.797</td></tr>
<tr><td>NPI</td><td>MD –1.52, 95%CI –3.68 to 0.63, P=0.166</td><td>MD –1.15, 95%CI –3.34 to 1.04, P=0.303</td></tr>
</table>
Adverse events
<table>
<tr><th></th><th>Donepezil 5mg (n=195)</th><th>Donepezil 10mg (n=182)</th><th>Placebo (n=173)</th></tr>
</table></td></tr>
</table>

Bibliographic reference	**Dubois,B., Tolosa,E., Katzenschlager,R., Emre,M., Lees,A.J., Schumann,G., Pourcher,E., Gray,J., Thomas,G., Swartz,J., Hsu,T., Moline,M.L., 20130214, Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study, Movement Disorders, 27, 1230-1238, 2012**
	<table><tr><td>All adverse events (%)</td><td>76.9</td><td>73.1</td><td>71.1</td></tr><tr><td>Adverse events leading to discontinuation (%)</td><td>13.8</td><td>17</td><td>11</td></tr><tr><td>Severe adverse events (%)</td><td>19</td><td>16.5</td><td>12.7</td></tr><tr><td>Visual hallucinations</td><td>5.1</td><td>0.5</td><td>1.2</td></tr></table>
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	None

Bibliographic reference	**Emre,M., Aarsland,D., Albanese,A., Byrne,E., Deuschl,G., De Deyn,P., Durif,F., Kulisevsky,J., van Laar,T., Lees,A., Poewe,W., Robillard,A., Rosa,M., Wolters,E., Quarg,P., Tekin,S., Lane,S., Rivastigmine for dementia associated with Parkinson's disease, N Engl J Med, 351, 2509-2518, 2004**
Full citation	Emre,M., Aarsland,D., Albanese,A., Byrne,E., Deuschl,G., De Deyn,P., Durif,F., Kulisevsky,J., van Laar,T., Lees,A., Poewe,W., Robillard,A., Rosa,M., Wolters,E., Quarg,P., Tekin,S., Lane,S., Rivastigmine for dementia associated with Parkinson's disease, N Engl J Med, 351, 2509-2518, 2004
Ref Id	Study not identified in literature search
Study type	Double-blind randomised controlled trial

Bibliographic reference	**Emre,M., Aarsland,D., Albanese,A., Byrne,E., Deuschl,G., De Deyn,P., Durif,F., Kulisevsky,J., van Laar,T., Lees,A., Poewe,W., Robillard,A., Rosa,M., Wolters,E., Quarg,P., Tekin,S., Lane,S., Rivastigmine for dementia associated with Parkinson's disease, N Engl J Med, 351, 2509-2518, 2004**
Aim of the study	To assess the efficacy and safety of rivastigmine in people with PDD
Country/ies where the study was carried out	Multicentre (Europe and Canada)
Study dates	Recruitment 2002-2003, study published 2004
Source of funding	Not stated in paper
Sample size	N=541 randomised
Inclusion criteria	People aged at least 50 years old with PDD (MMSE 10 to 24)
Exclusion criteria	Any primary neurodegenerative disorder other than PD or other causes of dementia, history of a major depressive episode, presence of an active, uncontrolled seizure disorder, presence of any disability or unstable disease unrelated to PD, known hypersensitivity to drugs similar to rivastigmine, use of a cholinesterase inhibitor or anticholinergic drugs during the 4 weeks before randomisation. No changes were permitted in the dose of current dopaminergic medicines within 4 weeks before and throughout the study, nor was the start of treatment with new psychotropic medications (except atypical neuroleptic agents for acute psychosis) permitted during this period
Details	Parallel group, 24-week double-blind, placebo-controlled RCT
Intervention(s)	Rivastigmine 1.5mg twice daily, increasing to a maximum well tolerated dose (up to 6mg twice daily)
Comparator(s)	Placebo
Results	Efficacy results at week 24

	n	Baseline (mean ± SD)	Change at 24 weeks (mean ± SD)	Between-group difference (value)	P value
Primary outcome					
ADAS-cog Rivastigmine Placebo	 329 161	 23.8±10.2 24.3±10.5	 –2.1±8.2 0.7±7.5	 2.90†	 <0.001
ADCS-CGIC Rivastigmine Placebo	 329 165	 — —	 3.8±1.4 4.3±1.5	 0.5	 0.007
Secondary outcomes					

Bibliographic reference	Emre,M., Aarsland,D., Albanese,A., Byrne,E., Deuschl,G., De Deyn,P., Durif,F., Kulisevsky,J., van Laar,T., Lees,A., Poewe,W., Robillard,A., Rosa,M., Wolters,E., Quarg,P., Tekin,S., Lane,S., Rivastigmine for dementia associated with Parkinson's disease, N Engl J Med, 351, 2509-2518, 2004

MMSE Rivastigmine Placebo	 335 166	 19.5±3.8 19.2±4.0	 0.8±3.8 –0.2±3.5	 1.00	 0.03
D-KEFS Rivastigmine Placebo	 258 144	 13.9±9.5 14.5±9.4	 1.7±6.8 –1.1±6.4	 2.80	 <0.001‡
CDR Rivastigmine Placebo	 328 158	 2197.0±1170.2 2490.5±2314.8	 –31.0±989.8 142.7±1780.2	 294.84†	 0.009
Clock drawing test Rivastigmine Placebo	 49 30	 3.4±3.7 2.9±3.8	 0.5±2.5 –0.6±2.4	 1.10	 0.02‡
ADCS-ADL Rivastigmine Placebo	 333 165	 41.6±18.6 41.2±17.7	 –1.1±12.6 –3.6±10.3	 2.50	 0.02
NPI Rivastigmine Placebo	 334 166	 12.7±11.7 13.2±13.0	 –2.0±10.0 0.0±10.4	 2.15†	 0.02

† The value is the modelled treatment difference (difference of least-square means)

‡ Because executive-function tests were not performed at all sites, analyses involving these tests included only patients who actually took these tests

Adverse events

	Rivastigmine (n=362) No. (%)	Placebo (n=179) No. (%)	P value
All adverse events	303 (83.7)	127 (70.9)	<0.001
Serious adverse events	(13)	(14.5)	0.69

Bibliographic reference	**Emre,M., Aarsland,D., Albanese,A., Byrne,E., Deuschl,G., De Deyn,P., Durif,F., Kulisevsky,J., van Laar,T., Lees,A., Poewe,W., Robillard,A., Rosa,M., Wolters,E., Quarg,P., Tekin,S., Lane,S., Rivastigmine for dementia associated with Parkinson's disease, N Engl J Med, 351, 2509-2518, 2004**
	Hallucinations | 17 (4.7) | 17 (9.5) | 0.04
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	Included in NICE CG35

Bibliographic reference	**Emre,M., Tsolaki,M., Bonuccelli,U., Destee,A., Tolosa,E., Kutzelnigg,A., Ceballos-Baumann,A., Zdravkovic,S., Bladstrom,A., Jones,R., Study,Investigators, 20101018, Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial, Lancet Neurology, 9, 969-977, 2010**
Full citation	Emre,M., Tsolaki,M., Bonuccelli,U., Destee,A., Tolosa,E., Kutzelnigg,A., Ceballos-Baumann,A., Zdravkovic,S., Bladstrom,A., Jones,R., Study,Investigators, 20101018, Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. [Review], Lancet Neurology, 9, 969-977, 2010
Ref Id	298618
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the efficacy and safety of memantine in in people with mild to moderate PDD or DLB
Country/ies where the study was carried out	Multicentre (UK, Germany, Austria, France, Greece, Italy, Spain, Turkey)
Study dates	Recruitment 2007-2008, study published 2010

Bibliographic reference	**Emre,M., Tsolaki,M., Bonuccelli,U., Destee,A., Tolosa,E., Kutzelnigg,A., Ceballos-Baumann,A., Zdravkovic,S., Bladstrom,A., Jones,R., Study,Investigators, 20101018, Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial, Lancet Neurology, 9, 969-977, 2010**
Source of funding	Lundbeck
Sample size	N=199 randomised
Inclusion criteria	People aged 50 years and older with PDD or DLB (MMSE score 10 to 24 inclusive) with a caregiver
Exclusion criteria	Cholinesterase inhibitors within 6 weeks before screening or memantine in the last 6 months, or any investigational drug within 30 days of screening. Psychiatric disorders, clinically significant or unstable systemic disease. Use of cholinesterase inhibitors, antipsychotic, antidepressant or benzodiazepine drugs were not allowed
Details	Parallel group, 24-week double-blind placebo-controlled RCT
Intervention(s)	Memantine 5mg daily, increasing to a maintenance dose of 20mg daily
Comparator(s)	Placebo
Results	Efficacy results at week 24 – people with PDD

Outcome	n	Change from baseline at 24 weeks Mean value (95%CI)	Between-group difference Mean value (95%CI)	P value
ADCS-CGIC				
Memantine	62	3.6 (3.3 to 4.0)	–0.1 (–0.6 to 0.3)	
Placebo	58	3.8 (3.4 to 4.1)		0.576
ADCS-ADL23				
Memantine	62	0.5 (–2.3 to 3.3)	0.7 (–3.0 to 4.5)	
Placebo	58	–0.3 (–3.3 to 2.8)		0.703
NPI				
Memantine	62	–1.6 (–4.9 to 1.8)	–1.4 (–5.9 to 3.0)	
Placebo	58	0.1 (–3.8 to 3.5)		0.522
UPDRS III				
Memantine	62	1.5 (–1.0 to 4.1)	0.6 (–2.6 to 3.8)	
Placebo	58	1.0 (–1.7 to 3.6)		0.719
ZBI				
Rivastigmine	62	–0.5 (–3.6 to 2.7)	–2.9 (–6.9 to 1.1)	
Placebo	58	2.4 (–0.8 to 5.7)		0.153

Bibliographic reference	**Emre,M., Tsolaki,M., Bonuccelli,U., Destee,A., Tolosa,E., Kutzelnigg,A., Ceballos-Baumann,A., Zdravkovic,S., Bladstrom,A., Jones,R., Study,Investigators, 20101018, Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial, Lancet Neurology, 9, 969-977, 2010**

Efficacy results at week 24 – people with DLB

Outcome	n	Change from baseline at 24 weeks Mean value (95%CI)	Between-group difference Mean value (95%CI)	P value
ADCS-CGIC				
Memantine	34	3.3 (2.8 to 3.8)	–0.6 (–1.2 to –0.1)	
Placebo	41	3.9 (3.5 to 4.3)		0.023
ADCS-ADL23				
Memantine	34	–0.1 (–5.2 to 5.1)	1.7 (–4.2 to 7.6)	
Placebo	41	–1.7 (–6.1 to 2.7)		0.569
NPI				
Memantine	34	–4.3 (–9.2 to 0.7)	–5.9 (–11.6 to –0.2)	
Placebo	41	1.7 (–2.5 to 5.9)		0.041
UPDRS III				
Memantine	34	1.5 (–1.0 to 4.1)	0.6 (–2.6 to 3.8)	
Placebo	41	1.0 (–1.7 to 3.6)		0.719
ZBI				
Rivastigmine	34	–0.5 (–3.6 to 2.7)	–2.9 (–6.9 to 1.1)	
Placebo	41	2.4 (–0.8 to 5.7)		0.153

Adverse events – people with PDD

	Memantine (n=62) No. (%)	Placebo (n=58) No. (%)
All adverse events	28 (45)	26 (45)
Serious adverse events	8 (13)	7 (12)
Adverse events leading to study withdrawal	6 (10)	5 (9)

Bibliographic reference	**Emre,M., Tsolaki,M., Bonuccelli,U., Destee,A., Tolosa,E., Kutzelnigg,A., Ceballos-Baumann,A., Zdravkovic,S., Bladstrom,A., Jones,R., Study,Investigators, 20101018, Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial, Lancet Neurology, 9, 969-977, 2010**
	Adverse events – people with DLB <table><tr><th></th><th>Memantine (n=34) No. (%)</th><th>Placebo (n=41) No. (%)</th></tr><tr><td>All adverse events</td><td>18 (53)</td><td>17 (41)</td></tr><tr><td>Serious adverse events</td><td>6 (18)</td><td>3 (7)</td></tr><tr><td>Adverse events leading to study withdrawal</td><td>5 (15)</td><td>7 (17)</td></tr></table>
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? YES 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? YES
Other information	None

Bibliographic reference	**Emre,M., Poewe,W., De Deyn,P.P., Barone,P., Kulisevsky,J., Pourcher,E., van,Laar T., Storch,A., Micheli,F., Burn,D., Durif,F., Pahwa,R., Callegari,F., Tenenbaum,N., Strohmaier,C., 20140911, Long-term safety of rivastigmine in Parkinson's disease dementia: an open-label, randomized study, Clinical Neuropharmacology, 37, 9-16, 2014**
Study type	Open-label randomised controlled trial
Aim of the study	To assess the safety of rivastigmine and effects on motor symptoms in people with mild to moderately severe PDD

<table>
<tr><th>Bibliographic reference</th><td>Emre,M., Poewe,W., De Deyn,P.P., Barone,P., Kulisevsky,J., Pourcher,E., van,Laar T., Storch,A., Micheli,F., Burn,D., Durif,F., Pahwa,R., Callegari,F., Tenenbaum,N., Strohmaier,C., 20140911, Long-term safety of rivastigmine in Parkinson’s disease dementia: an open-label, randomized study, Clinical Neuropharmacology, 37, 9-16, 2014</td></tr>
<tr><td>Country/ies where the study was carried out</td><td>Multicentre (Europe, USA, Argentina Canada and Australia)</td></tr>
<tr><td>Study dates</td><td>Recruitment 2008-2010, study published 2014</td></tr>
<tr><td>Source of funding</td><td>Novartis</td></tr>
<tr><td>Sample size</td><td>N=583 randomised</td></tr>
<tr><td>Inclusion criteria</td><td>People aged 50 to 85 years with PDD (MMSE score 10 to 26 inclusive) with caregiver support</td></tr>
<tr><td>Exclusion criteria</td><td>Other causes of dementia, Hoehn and Yahr stage of 5 in on-state, use of cholinesterase inhibitors or cholinergic drugs within 4 weeks before randomisation</td></tr>
<tr><td>Details</td><td>76-week prospective open-label RCT</td></tr>
<tr><td>Intervention(s)</td><td>Rivastigmine 4.6mg/24h patch, increasing to 9.5mg/24h patch</td></tr>
<tr><td>Comparator(s)</td><td>Rivastigmine 1.5mg twice daily, increasing to a maximum well tolerated dose (up to 6mg twice daily)</td></tr>
<tr><td>Results</td><td>Efficacy results
<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">Rivastigmine caps</th><th colspan="2">Rivastigmine patch</th><th rowspan="2">Least squares means difference (95%CI)</th><th rowspan="2">P value</th></tr>
<tr><th>n</th><th>Mean (SD)</th><th>n</th><th>Mean (SD)</th></tr>
<tr><td>MDRS
Baseline
Change from baseline at week 24
Change from baseline at week 76</td><td>
273
273
273</td><td>
109.5 (19.3)
6.5 (13.0)
3.9 (16.8)</td><td>
273
273
273</td><td>
109.4 (19.6)
4.4 (12.9)
–1.4 (17.4)</td><td>

2.3 (0.2 to 4.4)
5.5 (2.6 to 8.4)</td><td>

0.035
<0.001</td></tr>
<tr><td>ADCS-ADL
Baseline
Change from baseline at week 24
Change from baseline at week 76</td><td>
273
273
273</td><td>
49.2
–0.6 (10.1)
–4.4 (13.3)</td><td>
270
270
270</td><td>
50.1
–1.5 (10.9)
–7.8 (15.6)</td><td>

0.8 (–0.9 to 2.6)
3.4 (1.0 to 5.7)</td><td>

0.355
0.006</td></tr>
<tr><td>NPI</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table></td></tr>
</table>

Bibliographic reference	Emre,M., Poewe,W., De Deyn,P.P., Barone,P., Kulisevsky,J., Pourcher,E., van,Laar T., Storch,A., Micheli,F., Burn,D., Durif,F., Pahwa,R., Callegari,F., Tenenbaum,N., Strohmaier,C., 20140911, Long-term safety of rivastigmine in Parkinson's disease dementia: an open-label, randomized study, Clinical Neuropharmacology, 37, 9-16, 2014

Baseline Change from baseline at week 24 Change from baseline at week 76	273 273 273	11.3 (11.8) –2.6 (10.3) –1.6 (11.2)	273 273 273	11.4 (11.9) –1.0 (10.3) 0.7 (12.6)	 –1.7 (–3.2 to –0.1) –2.4 (–4.1 to –0.7)	 0.032 0.007
Note: Results for change from baseline at week 52 also reported in paper						

Adverse events

	Rivastigmine patch (n=288)	Rivastigmine capsules (n=294)
All adverse events (%)	91.3	93.2
Serious adverse events	28.8	29.6
Adverse events leading to study withdrawal (including deaths)	24.7	27.2
Deaths	24.7	27.2
Visual hallucinations	6.6	5.1

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? UNCLEAR
2. Was there adequate concealment of allocation? NO
3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES
4. Did the comparison groups receive the same care apart from interventions studied? YES
5. Were participants receiving care kept blind to treatment allocation? NO
6. Were the individuals administering care kept blind to treatment allocation? NO
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES
8. Did the study have an appropriate length of follow up? YES
9. Did the study use a precise definition of outcome? YES
10. Was a valid and reliable method used to determine that outcome? YES
11. Were investigators kept blind to participant's exposure to the intervention? NO

Bibliographic reference	**Emre,M., Poewe,W., De Deyn,P.P., Barone,P., Kulisevsky,J., Pourcher,E., van,Laar T., Storch,A., Micheli,F., Burn,D., Durif,F., Pahwa,R., Callegari,F., Tenenbaum,N., Strohmaier,C., 20140911, Long-term safety of rivastigmine in Parkinson's disease dementia: an open-label, randomized study, Clinical Neuropharmacology, 37, 9-16, 2014**
	12. Were investigators kept blind to other important confounding and prognostic factors? NO
Other information	None

Bibliographic reference	**Ikeda,M., Mori,E., Matsuo,K., Nakagawa,M., Kosaka,K., 20150225, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial, Alzheimer's Research & Therapy, 7, 4-, 2015**
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the efficacy of donepezil in people with DLB to confirm superiority over placebo
Country/ies where the study was carried out	Not stated in paper
Study dates	Not stated in paper, study published 2015
Source of funding	Eisai
Sample size	N=142 randomised
Inclusion criteria	People aged 50 years and older with DLB (MMSE score 10 to 26 inclusive) with caregiver support
Exclusion criteria	PD that was diagnosed at least 1 year prior to the onset of dementia; focal vascular lesions, other neurological or psychiatric diseases, clinically significant systemic disease, complications or a history of severe gastrointestinal ulcer, severe asthma or COPD, systolic hypotension, bradycardia, other significant cardiac problems, hypersensitivity to donepezil or piperidine derivatives, severe PD, treatment with cholinesterase inhibitors or any investigational drug within 3 months prior to screening. Cholinesterase inhibitors, antipsychotics and anti-Parkinson's drugs other than levodopa or dopamine agonists were not allowed during the study
Details	Parallel group, 12-week double-blind placebo-controlled RCT
Intervention(s)	Donepezil 5mg or 10mg daily
Comparator(s)	Placebo
Results	Efficacy results at week 12

Co-primary outcomes				
	n	Baseline Mean value ± SD	Change at week 12 (LOCF) Mean value ± SD	P value
MMSE				

Bibliographic reference	Ikeda,M., Mori,E., Matsuo,K., Nakagawa,M., Kosaka,K., 20150225, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial, Alzheimer's Research & Therapy, 7, 4-, 2015

Placebo Donepezil 5mg Donepezil 10mg	44 45 49	20.3 ± 4.2 20.6 ± 4.1 20.3 ± 4.8	0.6 ± 3.0 1.4 ± 3.4 2.2 ± 2.9	 0.232 0.016
NPI-2 Placebo Donepezil 5mg Donepezil 10mg	 44 45 49	 6.9 ± 4.5 6.9 ± 4.5 7.3 ± 4.7	 –2.0 ± 4.2 –1.7 ± 4.3 –2.9 ± 4.7	 0.661 0.391
Secondary outcomes				
	n	Baseline Mean value ± SE	Change at week 12 (LOCF) Mean value ± SE	P value
NPI Placebo Donepezil 5mg Donepezil 10mg	 44 45 49	 –20.5 ± 15.0 –18.9 ± 15.3 –16.6 ± 11.7	 –6.4 ± 1.5 –3.3 ± 1.4 –5.5 ± 1.4	 0.143 0.660
UPDRS III Placebo Donepezil 5mg Donepezil 10mg	 44 45 49	Data not reported	 –0.9 ± 0.9 –1.7 ± 0.9 –0.4 ± 0.9	 0.525 0.306
ZBI Placebo Donepezil 5mg Donepezil 10mg	 44 45 49	 28.4 ± 16.2 28.3 ± 18.5 31.4 ± 17.8	 –0.1 ± 1.8 –5.0 ± 1.8 –0.8 ± 1.7	 NS NS
NPI-2; 2 domains of NPI - hallucinations and cognitive fluctuations NS; No significant difference between groups, but P value not reported in paper				

Adverse events

Bibliographic reference	**Ikeda,M., Mori,E., Matsuo,K., Nakagawa,M., Kosaka,K., 20150225, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial, Alzheimer's Research & Therapy, 7, 4-, 2015**

	Donepezil 5mg (n=47) No. (%)	Donepezil 10mg (n=49) No. (%)	Placebo (n=46) No. (%)
All adverse events	30 (63.8)	34 (69.4)	31 (67.4)
Treatment-related adverse events	12 (25.5)	14 (28.6)	11 (23.9)
Serious adverse events	4 (8.5)	1 (2.0)	5 (10.9)
Withdrawal due to adverse events	10 (21.3)	1 (2.0)	5 (10.9)

Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? NO 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	None

Bibliographic reference	**Leroi,I., Overshott,R., Byrne,E.J., Daniel,E., Burns,A., 20090917, Randomized controlled trial of memantine in dementia associated with Parkinson's disease, Movement Disorders, 24, 1217-1221, 2009**
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the safety and tolerability of memantine in people with PDD
Country/ies where the study was carried out	UK
Study dates	Not stated in paper, study published 2009

<table>
<tr><th>Bibliographic reference</th><th>Leroi,I., Overshott,R., Byrne,E.J., Daniel,E., Burns,A., 20090917, Randomized controlled trial of memantine in dementia associated with Parkinson's disease, Movement Disorders, 24, 1217-1221, 2009</th></tr>
<tr><td>Source of funding</td><td>Lundbeck</td></tr>
<tr><td>Sample size</td><td>N=25 randomised</td></tr>
<tr><td>Inclusion criteria</td><td>People with PDD (MMSE score 10 to 27). Those taking cholinesterase inhibitors (2 people in each group) had to have been stable on the medication for at least 6 months prior to study entry with no recorded improvement in cognitive and behavioural symptoms for at least 4 weeks prior to randomisation.</td></tr>
<tr><td>Exclusion criteria</td><td>Known sensitivity to NMDA receptor antagonists, current use of amantadine, ranitidine or cimetidine, brain disease other than PD, history of neurosurgery, meeting criteria for probable DLB</td></tr>
<tr><td>Details</td><td>Parallel group, 22-week double-blind, placebo-controlled RCT. Memantine was discontinued at week 16 with final evaluation (off-drug) at week 22</td></tr>
<tr><td>Intervention(s)</td><td>Memantine 20mg daily</td></tr>
<tr><td>Comparator(s)</td><td>Placebo</td></tr>
<tr><td>Results</td><td>Efficacy results
<table>
<tr><th></th><th colspan="3">Placebo mean (SD)</th><th colspan="3">Memantine mean (SD)</th><th colspan="3">Difference in mean scores between baseline and end of drug treatment</th></tr>
<tr><th>Outcome</th><th>Baseline</th><th>Week 16a</th><th>Week 22b</th><th>Baseline</th><th>Week 16a</th><th>Week 22b</th><th>Deltac</th><th>Delta 95%CI</th><th>P value</th></tr>
<tr><td>MMSE</td><td>18.9 (6.2)</td><td>20.9 (6.0)</td><td>18.5 (6.7)</td><td>19.3 (5.9)</td><td>19.9 (6.3)</td><td>16.9 (7.2)</td><td>–1.5</td><td>–4.9 to 1.3</td><td>0.2</td></tr>
<tr><td>DRS</td><td>94.1 (38.5)</td><td>100.3 (33.9)</td><td>101.2 (37.5)</td><td>88.4 (31.7)</td><td>94.7 (32.8)</td><td>92.0 (28.4)</td><td>0.1</td><td>–19.3 to 19.6</td><td>1.0</td></tr>
<tr><td>NPI</td><td>14.3 (10.6)</td><td>13.5 (12.4)</td><td>19.6 (11.0)</td><td>14.9 (10.9)</td><td>11.5 (11.5)</td><td>18.2 (14.6)</td><td>–2.6</td><td>–15.6 to 10.3</td><td>0.7</td></tr>
<tr><td>UPDRS III</td><td>23.8 (10.1)</td><td>21.9 (9.1)</td><td>48.8 (15.1)</td><td>24.6 (10.0)</td><td>24.3 (8.8)</td><td>46.3 (19.9)</td><td>1.6</td><td>–1.4 to 4.7</td><td>0.3</td></tr>
<tr><td colspan="10">a Week 16 was the end of drug treatment
b Week 22 was the end of the 6-week drug withdrawal phase
c Delta value = (end of study drug memantine – baseline memantine) – (end of study drug placebo – baseline placebo)</td></tr>
</table>
At week16, in mean CIBIC+ in the memantine group was 60% vs. 43% in the placebo group (χ2= 5.4, df 2, P=0.07). After 6 weeks off the study drug (week 22), 70% of the memantine treated participants deteriorated compared with 29% of people</td></tr>
</table>

Bibliographic reference	Leroi,I., Overshott,R., Byrne,E.J., Daniel,E., Burns,A., 20090917, Randomized controlled trial of memantine in dementia associated with Parkinson's disease, Movement Disorders, 24, 1217-1221, 2009
	treated with placebo (χ2=4.0, df1, P =0.04). The magnitude of this deterioration was significantly greater in the memantine group vs. placebo (mean CIBIC+ score 5.4 (SD 1.2) vs. 4.4 (SD 0.5), respectively) (t=3.2, df22, P=0.004) Adverse events There were 2 serious adverse events (1 in each group), which were considered unlikely to have been related to study medication. Placebo / Memantine Minor adverse events (%): 54.5 / 64.3
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	None

Bibliographic reference	McKeith,I., Del,Ser T., Spano,P., Emre,M., Wesnes,K., Anand,R., Cicin-Sain,A., Ferrara,R., Spiegel,R., Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study, Lancet.356 (9247) (pp 2031-2036), 2000.Date of Publication: 16 Dec 2000., 2031-2036, 2000
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the efficacy, tolerability and safety of rivastigmine in people with DLB

Bibliographic reference	**McKeith,I., Del,Ser T., Spano,P., Emre,M., Wesnes,K., Anand,R., Cicin-Sain,A., Ferrara,R., Spiegel,R., Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study, Lancet.356 (9247) (pp 2031-2036), 2000.Date of Publication: 16 Dec 2000., 2031-2036, 2000**
Country/ies where the study was carried out	Spain, UK and Italy
Study dates	Not stated in paper, study published 2000
Source of funding	Not stated in paper
Sample size	N=120 randomised
Inclusion criteria	People with DLB (MMSE score over 9) with caregiver support
Exclusion criteria	Severe extrapyramidal symptoms, asthma, known hypersensitivity to rivastigmine or similar drugs. Neuroleptics, anticholinergics, selegiline or similar drugs were not allowed
Details	Parallel group, 20-week double-blind, placebo-controlled RCT
Intervention(s)	Rivastigmine 1.5mg twice daily, increasing to a maximum well tolerated dose (up to 6mg twice daily)
Comparator(s)	Placebo
Results	Efficacy results at week 20

	n	Baseline mean (SD)	Change from baseline at 20 weeks (SD)	Between-group difference (95%CI)	P value
Primary outcome – NPI-4					
ITT Rivastigmine Placebo	 59 61	 12.2 (8.2) 11.7 (8.6)	 2.5 (8.4) 0.8 (7.3)	1.7 (–1.1 to 4.6)	0.088
LOCF Rivastigmine Placebo	 47 53	 12.1 (7.9) 11.2 (8.4)	 3.1 (9.1) 0.8 (7.4)	2.3 (–0.9 to 5.7)	0.045
OC Rivastigmine Placebo	 41 51	 12.0 (7.9) 11.3 (8.6)	 4.1 (8.3) 0.7 (7.4)	3.4 (0.06 to 6.6)	0.010
NPI-10					
LOCF Rivastigmine	 47	 23.2 (15.0)	 5.0 (16.2)	3.8 (–1.6 to 9.2)	0.048

Bibliographic reference	McKeith,I., Del,Ser T., Spano,P., Emre,M., Wesnes,K., Anand,R., Cicin-Sain,A., Ferrara,R., Spiegel,R., Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study, Lancet.356 (9247) (pp 2031-2036), 2000.Date of Publication: 16 Dec 2000., 2031-2036, 2000

Placebo	53	20.2 (14.2)	1.2 (10.7)		
OC Rivastigmine Placebo	 41 51	 22.7 (15.0) 20.1 (14.4)	 7.3 (13.7) 0.9 (10.4)	 6.4 (1.4 to 11.5)	 0.005
ITT; Intention to treat dataset, LOCF; Last observation carried forward dataset, OC; Observed cases dataset					

There were no significant differences between groups in MMSE, CGC+ score and UPDRS III (data not reported in paper)

	Placebo (n=61)	Rivastigmine (n=59)
Adverse events (%)	46 (75%)	54 (92%)
Severe adverse events	8 (13%)	10 (17%)

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? YES
2. Was there adequate concealment of allocation? UNCLEAR
3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES
4. Did the comparison groups receive the same care apart from interventions studied? YES
5. Were participants receiving care kept blind to treatment allocation? YES
6. Were the individuals administering care kept blind to treatment allocation? YES
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES
8. Did the study have an appropriate length of follow up? YES
9. Did the study use a precise definition of outcome? YES
10. Was a valid and reliable method used to determine that outcome? YES
11. Were investigators kept blind to participant's exposure to the intervention? YES
12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR

Other information: Included in CG42

Bibliographic reference	**Mori,E., Ikeda,M., Kosaka,K., Donepezil-DLB,Study,I, 20121024, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial, Annals of Neurology, 72, 41-52, 2012**
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the efficacy and safety of donepezil in 3 different doses compared with placebo, in people with DLB
Country/ies where the study was carried out	Japan
Study dates	Recruitment 2007-2010, study published 2012
Source of funding	Not stated in paper
Sample size	N=140 randomised
Inclusion criteria	People aged 50 years and older with DLB (MMSE score 10 to 26 inclusive) with caregiver support
Exclusion criteria	PD diagnosed at least 1 year prior to the onset of dementia, focal vascular lesions that might cause cognitive impairment, other neurological or psychiatric diseases, clinically significant systemic disease, complications or history of severe gastrointestinal ulcer, severe asthma or COPD, systolic hypotension and other significant CV problems (e.g. QT interval prolongation), hypersensitivity to donepezil or piperidine derivatives, severe PD, treatment with cholinesterase inhibitors or any investigational drug within 3 months prior to screening. Cholinesterase inhibitors, antipsychotics, and antiparkinsonian drugs other than levodopa or dopamine agonists were not allowed.
Details	Parallel group, 12-week double blind, placebo controlled RCT
Intervention(s)	Donepezil 3mg, 5mg or 10mg daily
Comparator(s)	Placebo
Results	Efficacy results for donepezil

	Baseline			Change				
Outcome	n	Mean (SD)	P (ANOVA)	n	Mean (SD)	Difference (95%CI)	P value (t test)	P value (ANCOVA)
MMSE								
Placebo	32	18.3 (4.7)	0.271	31	–0.4 (2.7)			
3mg	35	20.4 (4.1)		35	1.6 (3.8)	2.0 (0.4 to 3.7)	0.017	0.013
5mg	32	19.8 (4.4)		32	3.4 (3.2)	3.8 (2.3 to 5.3)	<0.001	<0.001
10mg	36	19.8 (4.4)		36	2.0 (3.3)	2.4 (0.9 to 3.9)	0.001	<0.001
NPI								
Placebo	32	18.3 (8.9)	0.079	32	0.3 (17.5)			

Bibliographic reference	Mori,E., Ikeda,M., Kosaka,K., Donepezil-DLB,Study,I, 20121024, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial, Annals of Neurology, 72, 41-52, 2012								
	3mg	35	20.7 (12.8)		35	–3.9 (22.0)	–4.2 (–13.9 to 5.6)	0.396	0.602
	5mg	32	14.0 (8.3)		32	–5.5 (6.7)	–5.8 (–12.4 to 0.8)	0.086	0.047
	10mg	36	19.5 (12.8)		35	–8.0 (12.8)	–8.3 (–15.8 to –0.9)	0.029	0.019
	NPI-2								
	Placebo	32	6.3 (4.0)	0.443	32	1.1 (5.7)			
	3mg	35	7.1 (4.1)		35	–2.1 (6.3)	–3.2 (–6.1 to –0.3)	0.032	0.025
	5mg	32	6.3 (4.8)		32	–3.3 (3.8)	–4.4 (–6.8 to –2.0)	<0.001	<0.001
	10mg	36	7.9 (5.4)		35	–4.6 (4.5)	–5.8 (–8.2 to –3.3)	<0.001	<0.001
	NPI-4								
	Placebo	32	12.1 (6.3)	0.269	32	–0.3 (8.5)			
	3mg	35	11.5 (7.0)		35	–2.4 (10.8)	–2.1 (–6.9 to 2.6)	0.377	0.261
	5mg	32	9.0 (5.3)		32	–4.2 (4.9)	–3.9 (–7.3 to –0.4)	0.028	0.008
	10mg	36	11.9 (8.8)		35	–5.1 (7.4)	–4.8 (–8.7 to –1.0)	0.015	0.006
	ZBI								
	Placebo	32	21.8 (10.1)	0.197	31	4.2 (10.4)			
	3mg	35	27.9 (13.9)		33	–1.3 (13.2)	–5.5 (–11.5 to 0.5)	0.069	0.301
	5mg	32	22.9 (11.5)		31	–0.7 (15.7)	–4.9 (–11.7 to 1.8)	0.149	0.172
	10mg	36	26.5 (16.1)		31	–5.0 (13.6)	–9.2 (–15.3 to –3.0)	0.004	0.035
	UPDRS III								
	Placebo	33	20.8 (10.6)	0.702	31	0.7 (3.8)			
	3mg	35	17.9 (9.0)		34	–0.5 (7.4)	–1.3 (–4.2 to 1.7)	0.393	0.397
	5mg	33	19.1 (10.7)		32	–0.5 (5.4)	–1.3 (–3.6 to 1.1)	0.281	0.358
	10mg	37	18.9 (11.6)		33	–1.0 (6.7)	–1.8 (–4.5 to 1.0)	0.200	0.258
	NPI-2; 2 domains of NPI – hallucinations + cognitive fluctuation NPI-4; 4 domains of NPI – delusions + hallucinations + dysphoria + apathy								

	Mean CIBIC+ score (range 1-7)	P value (difference from placebo)

Bibliographic reference	Mori,E., Ikeda,M., Kosaka,K., Donepezil-DLB,Study,I, 20121024, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial, Annals of Neurology, 72, 41-52, 2012

Placebo	3.73	—
Donepezil 3mg	4.78	0.010
Donepezil 5mg	5.03	0.004
Donepezil 10mg	4.86	0.034

Adverse events

	Placebo (n=34)	3mg (n=35)	5mg (n=33)	10mg (n=37)
All adverse events (%)	24 (71)	24 (69)	27 (82)	32 (87)
Serious adverse events (%)	2 (5.9)	2 (5.7)	2 (6.1)	4 (10.8)
Adverse events leading to study withdrawal (%)	4 (11.8)	3 (8.6)	1 (3.0)	3 (8.1)
No statistically significant differences between placebo and each active group				

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? YES
2. Was there adequate concealment of allocation? UNCLEAR
3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES
4. Did the comparison groups receive the same care apart from interventions studied? YES
5. Were participants receiving care kept blind to treatment allocation? YES
6. Were the individuals administering care kept blind to treatment allocation? YES
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES
8. Did the study have an appropriate length of follow up? YES
9. Did the study use a precise definition of outcome? YES
10. Was a valid and reliable method used to determine that outcome? YES
11. Were investigators kept blind to participant's exposure to the intervention? YES
12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR

Other information: None

<table>
<tr><th>Bibliographic reference</th><td>Ravina,B., Putt,M., Siderowf,A., Farrar,J.T., Gillespie,M., Crawley,A., Fernandez,H.H., Trieschmann,M.M., Reichwein,S., Simuni,T., 20050719, Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study, Journal of Neurology, Neurosurgery & Psychiatry, 76, 934-939, 2005</td></tr>
<tr><td>Study type</td><td>Double-blind randomised controlled trial</td></tr>
<tr><td>Aim of the study</td><td>To assess the safety and efficacy of donepezil in people with PDD</td></tr>
<tr><td>Country/ies where the study was carried out</td><td>USA</td></tr>
<tr><td>Study dates</td><td>Not stated in paper, study published 2005</td></tr>
<tr><td>Source of funding</td><td>National Institutes of Neurological Disorders and Stroke, National Institute on Aging</td></tr>
<tr><td>Sample size</td><td>N=22 randomised</td></tr>
<tr><td>Inclusion criteria</td><td>People aged 40 years and older with PDD (MMSE score 17 to 26 inclusive)</td></tr>
<tr><td>Exclusion criteria</td><td>Other causes of dementia, pregnancy or lactation, use of cholinergic or anticholinergic drugs (except amantadine or tolterodine within 2 weeks prior to screening), medical conditions or uncontrolled psychosis that would interfere with the safe conduct of the study</td></tr>
<tr><td>Details</td><td>26-week double blind, placebo-controlled crossover RCT. Participants were randomised to either donepezil or placebo for 10 weeks, with a 6-week washout period prior to crossover treatment for a further 10 weeks</td></tr>
<tr><td>Intervention(s)</td><td>Donepezil 5mg daily or 5mg twice daily</td></tr>
<tr><td>Comparator(s)</td><td>Placebo</td></tr>
<tr><td>Results</td><td>Efficacy results after 10 weeks treatment
<table>
<tr><th>Outcome</th><th>Donepezil
Mean score (SD)</th><th>Placebo
Mean score (SD)</th><th>Treatment effect (SE)</th><th>P value</th><th>Adjusted P valuea</th></tr>
<tr><td>ADAS-cog</td><td>22.5 (6.9)</td><td>24.4 (9.4)</td><td>–1.9 (1.4)</td><td>0.18</td><td>0.54</td></tr>
<tr><td>MMSE</td><td>24.5 (3.2)</td><td>22.5 (4.7)</td><td>2.0 (0.61)</td><td>0.0044</td><td>0.018</td></tr>
<tr><td>MDRS</td><td>108.3 (17.1)</td><td>108.5 (18.2)</td><td>–0.2 (1.9)</td><td>0.98</td><td>0.98</td></tr>
<tr><td>CGI</td><td>3.58 (0.77)</td><td>3.95 (0.85)</td><td>–0.37 (N/A)</td><td>0.0056</td><td>0.022</td></tr>
<tr><td>UPDRS III</td><td>40.3 (13.6)</td><td>40.5 (13.7)</td><td>—</td><td>0.76</td><td>—</td></tr>
<tr><td colspan="6">a Adjusted for multiple comparisons using Hommel method</td></tr>
</table>
Adverse events</td></tr>
</table>

Bibliographic reference	**Ravina,B., Putt,M., Siderowf,A., Farrar,J.T., Gillespie,M., Crawley,A., Fernandez,H.H., Trieschmann,M.M., Reichwein,S., Simuni,T., 20050719, Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study, Journal of Neurology, Neurosurgery & Psychiatry, 76, 934-939, 2005**
	<table><tr><th></th><th>Donepezil (n=21)</th><th>Placebo (n=20)</th><th>P value</th></tr><tr><td>Tolerability (%)</td><td>17 (81)</td><td>18 (90)</td><td>0.41</td></tr><tr><td>All adverse events (%)</td><td>11 (52)</td><td>9 (45)</td><td>0.64</td></tr><tr><td colspan="4">Tolerability was defined as the proportion of study participants remaining on study drug for the full period</td></tr></table>
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	Included in NICE CG35