G.7.3 Pharmacological management of Parkinson's disease dementia

- What is the comparative effectiveness of donepezil, galantamine, memantine and rivastigmine for cognitive enhancement in dementia associated with Parkinson's disease?

G.7.3.1 Parkinson's disease dementia – cholinesterase inhibitors

PDD – cholinesterase inhibitor vs. placebo: adverse events

Quality assessment						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	ChI	Placebo	Relative (95% CI)	Absolute (95% CI)	
Any adverse events – cholinesterase inhibitors (probability of experiencing ≥1; follow-up 10 to 24 weeks; lower is better)										
4[1–4]	RCT	not serious	not serious	not serious	serious[5]	609/774 (78.7%)	268/384 (69.8%)	RR 1.12 (1.04 to 1.21)	84 more per 1000 (from 28 more to 147 more)	⊕⊕⊕O MODERATE
Any adverse events – donepezil (probability of experiencing ≥1; follow-up 10 to 24 weeks; lower is better)										
3[1,2,4]	RCT	not serious	not serious	not serious	serious[5]	306/412 (74.3%)	141/205 (68.8%)	RR 1.07 (0.96 to 1.19)	48 more per 1000 (from 28 fewer to 131 more)	⊕⊕⊕O MODERATE
Any adverse events – rivastigmine (probability of experiencing ≥1; follow-up 24 weeks; lower is better)										
1[3]	RCT	not serious	N/A	not serious	not serious	303/362 (83.7%)	127/179 (70.9%)	RR 1.18 (1.06 to 1.31)	128 more per 1000 (from 43 more to 220 more)	⊕⊕⊕⊕ HIGH
Serious adverse events – cholinesterase inhibitors (probability of experiencing ≥1; follow-up 24 weeks; lower is better)										
2[2,3]	RCT	not serious	serious[6]	not serious	serious[5]	114/739 (15.4%)	48/352 (13.6%)	RR 1.12 (0.72 to 1.73)	18 more per 1000 (from 39 fewer to 100 more)	⊕⊕OO LOW
Serious adverse events – donepezil (probability of experiencing ≥1; follow-up 24 weeks; lower is better)										
1[2]	RCT	not serious	N/A	not serious	serious[5]	67/377 (17.8%)	22/173 (12.7%)	RR 1.4 (0.89 to 2.18)	51 more per 1000 (from 14 fewer to 150 more)	⊕⊕⊕O MODERATE
Serious adverse events – rivastigmine (probability of experiencing ≥1; follow-up 24 weeks; lower is better)										
1[3]	RCT	not serious	N/A	not serious	serious[5]	47/362 (13%)	26/179 (14.5%)	RR 0.89 (0.57 to 1.39)	16 fewer per 1000 (from 62 fewer to 57 more)	⊕⊕⊕O MODERATE
Adverse events requiring treatment withdrawal – cholinesterase inhibitors (probability of experiencing; follow-up 24 weeks; lower is better)										
3[1–3]	RCT	not serious	not serious	not serious	serious[5]	122/753 (16.2%)	33/364 (9.1%)	RR 1.76 (1.23 to 2.53)	69 more per 1000 (from 21 more to 139 more)	⊕⊕⊕O MODERATE
Adverse events requiring treatment withdrawal – donepezil (probability of experiencing; follow-up 24 weeks)										
2[1,2]	RCT	not serious	not serious	not serious	serious[5]	60/391 (15.3%)	19/185 (10.3%)	RR 1.46 (0.91 to 2.35)	47 more per 1000 (from 9 fewer to 139 more)	⊕⊕⊕O MODERATE
Adverse events requiring treatment withdrawal – rivastigmine (probability of experiencing; follow-up 24 weeks)										
1[3]	RCT	not serious	N/A	not serious	not serious	62/362 (17.1%)	14/179 (7.8%)	RR 2.19 (1.26 to 3.8)	93 more per 1000 (from 20 more to 219 more)	⊕⊕⊕⊕ HIGH

Quality assessment						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Chl	Placebo	Relative (95% CI)	Absolute (95% CI)	
Hallucinations – cholinesterase inhibitors (probability of experiencing; follow-up 24 weeks; lower is better)										
2[2,3]	RCT	not serious	not serious	not serious	serious[5]	35/739 (4.7%)	31/352 (8.8%)	RR 0.54 (0.34 to 0.86)	41 fewer per 1000 (from 12 fewer to 58 fewer)	⊕⊕⊕O MODERATE
Hallucinations – donepezil (probability of experiencing; follow-up 24 weeks; lower is better)										
1[2]	RCT	not serious	N/A	not serious	serious[5]	18/377 (4.8%)	14/173 (8.1%)	RR 0.59 (0.3 to 1.16)	33 fewer per 1000 (from 57 fewer to 13 more)	⊕⊕⊕O MODERATE
Hallucinations – rivastigmine (probability of experiencing; follow-up 24 weeks; lower is better)										
1[3]	RCT	not serious	N/A	not serious	serious[5]	17/362 (4.7%)	17/179 (9.5%)	RR 0.49 (0.26 to 0.95)	48 fewer per 1000 (from 5 fewer to 70 fewer)	⊕⊕⊕O MODERATE

[1] Aarsland 2002
[2] Dubois 2012; data for 2 active treatment groups were combined (donepezil 5mg and 10mg)
[3] Emre 2004
[4] Ravina 2005
[5] At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference
[6] i^2 > 40% between studies

PDD – rivastigmine patches vs. rivastigmine capsules: adverse events

Quality assessment						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivastigmine patches	Rivastigmine capsules	Relative (95% CI)	Absolute (95%CI)	
Any adverse events (probability of experiencing ≥1; follow-up 76 weeks; lower is better)										
1[1]	RCT	serious[2]	N/A	not serious	not serious	263/288 (91.3%)	274/294 (93.2%)	RR 0.98 (0.93 to 1.03)	19 fewer per 1000 (from 65 fewer to 28 more)	⊕⊕OO LOW
Serious adverse events (probability of experiencing ≥1; follow-up 76 weeks; lower is better)										
1[1]	RCT	serious[2]	N/A	not serious	serious[3]	83/288 (28.8%)	87/294 (29.6%)	RR 0.97 (0.76 to 1.25)	9 fewer per 1000 (from 71 fewer to 74 more)	⊕⊕OO LOW
Adverse events requiring treatment withdrawal (probability of experiencing; follow-up 76 weeks; lower is better)										
1[1]	RCT	serious[2]	N/A	not serious	serious[3]	71/288 (24.7%)	80/294 (27.2%)	RR 0.91 (0.69 to 1.19)	24 fewer per 1000 (from 84 fewer to 52 more)	⊕⊕OO LOW
Hallucinations (probability of experiencing ; follow-up 76 weeks)										
1[1]	RCT	serious[2]	N/A	not serious	serious[3]	25/288 (8.7%)	20/294 (6.8%)	RR 1.28 (0.73 to 2.25)	19 more per 1000 (from 18 fewer to 85 more)	⊕⊕OO LOW

[1] Emre 2014
[2] Open-label study
[3] Data are consistent with appreciable harm, appreciable benefit or no difference

PDD – cholinesterase inhibitor vs. placebo: cognitive function

Quality assessment						No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Chl	Placebo	Mean difference (95% CI)	
MMSE – cholinesterase inhibitors (follow-up 10 to 24 weeks; range of scores: 0-30; higher is better)									
4[1–4]	RCT	not serious	not serious	not serious	not serious	752	367	1.36 higher (0.95 to 1.77 higher)	⊕⊕⊕⊕ HIGH
MMSE – donepezil (follow-up 10 to 24 weeks; range of scores: 0-30; higher is better)									
3[1,2,4]	RCT	not serious	not serious	not serious	not serious	417	201	1.58 higher (1.06 to 2.1 higher)	⊕⊕⊕⊕ HIGH
MMSE – rivastigmine (follow-up 24 weeks; range of scores: 0-30; higher is better)									
1[3]	RCT	not serious	N/A	not serious	not serious	335	166	1 higher (0.33 to 1.67 higher)	⊕⊕⊕⊕ HIGH
ADAS-cog – cholinesterase inhibitors (follow-up 10 to 24 weeks; range of scores: 0-70; lower is better)									
3[1,2,4]	RCT	not serious	not serious	not serious	not serious	689	346	2.28 lower (3.40 to 1.15 lower)	⊕⊕⊕⊕ HIGH
ADAS-cog – donepezil (follow-up 10 to 24 weeks; range of scores: 0-70; lower is better)									
2[2,4]	RCT	not serious	not serious	not serious	serious[5]	360	185	1.5 lower (3.28 lower to 0.27 higher)	⊕⊕⊕O MODERATE
ADAS-cog – rivastigmine (follow-up 24 weeks; range of scores: 0-70; lower is better)									
1[3]	RCT	not serious	N/A	not serious	not serious	329	161	2.8 lower (4.26 to 1.34 lower)	⊕⊕⊕⊕ HIGH
MDRS (total score) – cholinesterase inhibitors (follow-up 10 to 24 weeks; range of scores: 0-144; higher is better)[6]									
2[3,4]	RCT	not serious	not serious	not serious	very serious[5,7]	35	31	3.39 higher (4.06 lower to 10.84 higher)	⊕⊕OO LOW
MDRS (total score) – donepezil (follow-up 10 weeks; range of scores: 0-144; higher is better)									
1[4]	RCT	not serious	N/A	not serious	very serious[5,7]	19	19	0.2 lower (11.44 lower to 11.04 higher)	⊕⊕OO LOW
MDRS (total score) – rivastigmine (follow-up 24 weeks; range of scores: 0-144; higher is better)[6]									
1[3]	RCT	serious[7]	N/A	not serious	serious[5]	16	12	6.21 higher (3.75 lower to 16.17 higher)	⊕⊕OO LOW
Clock drawing test – rivastigmine (follow-up 24 weeks; range of scores: 0-10; higher is better)									
1[3]	RCT	serious[7]	N/A	not serious	serious[5]	49	30	1.1 higher (0.01 lower to 2.21 higher)	⊕⊕OO LOW
D-KEFS verbal fluency test (total score) – rivastigmine (follow-up 24 weeks; measured by number of correct responses; higher is better)									
1[3]	RCT	not serious	N/A	not serious	not serious	258	144	2.8 higher (1.47 to 4.13 higher)	⊕⊕⊕⊕ HIGH
D-KEFS verbal fluency test (letter fluency) – donepezil (follow-up 24 weeks; higher is better)									

Quality assessment						No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Chl	Placebo	Mean difference (95% CI)	
1[2]	RCT	not serious	N/A	not serious	not serious	307	152	2.83 higher (0.95 to 4.71 higher)	⊕⊕⊕⊕ HIGH
D-KEFS verbal fluency test (category fluency) – donepezil (follow-up 24 weeks; higher is better)									
1[2]	RCT	not serious	N/A	not serious	not serious	307	152	3.93 higher (2.05 to 5.81 higher)	⊕⊕⊕⊕ HIGH
D-KEFS verbal fluency test (category switching) – donepezil (follow-up 24 weeks; higher is better)									
1[2]	RCT	not serious	N/A	not serious	serious[5]	307	152	1.09 higher (0.79 lower to 2.97 higher)	⊕⊕⊕O MODERATE
CDR – rivastigmine (follow-up 24 weeks; measured with: milliseconds; lower is better)									
1[3]	RCT	not serious	N/A	not serious	serious[5]	328	158	173.7 lower (471.23 lower to 123.83 higher)	⊕⊕⊕O MODERATE
BTA – donepezil (follow-up 24 weeks; range of scores: 0-20; higher is better)									
1[2]	RCT	serious[8]	N/A	not serious	not serious	221	111	0.88 higher (0.4 to 1.37 higher)	⊕⊕⊕O MODERATE

[1] Aarsland 2002
[2] Dubois 2012; data for 2 active treatment groups were combined (donepezil 5mg and 10mg). Mean and standard deviation calculated from data reported in paper
[3] Emre 2004
[4] Ravina 2005
[5] At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference
[6] Data from Emre 2004 reported in a secondary publication (Dujardin 2006)
[7] Small numbers of participants in the analysis
[8] Data available for only a small proportion of all participants for this outcome

PDD – rivastigmine patches vs. rivastigmine capsules: cognitive outcomes

Quality assessment						No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivastigmine patches	Rivastigmine capsules	Mean difference (95% CI)	
MDRS (total score) (follow-up 24 weeks; range of scores 0-144; higher is better)									
1[1]	RCT	serious[2]	N/A	not serious	serious[3]	273	273	2.1 lower (4.27 lower to 0.07 higher)	⊕⊕OO LOW
MDRS (total score) (follow-up 76 weeks; range of scores 0-144; higher is better)									
1[1]	RCT	serious[2]	N/A	not serious	not serious	273	273	5.3 lower (8.17 to 2.43 lower)	⊕⊕⊕O MODERATE

[1] Emre 2014
[2] Open-label study
[3] At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference

PDD – cholinesterase inhibitor vs. placebo: global assessment

Quality assessment						No of patients		Effect (95%CI)	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	ChI	Placebo		
Global function – cholinesterase inhibitors (follow-up 10 to 24 weeks; measured with: CIBIC+, ADCS-CGIC or CGIC; range of scores: 1-7; lower is better)									
4[1–4]	RCT	not serious	not serious	not serious	serious[5]	707	366	SMD 0.3 lower (0.42 to 0.17 lower)	⊕⊕⊕O MODERATE
Global response – cholinesterase inhibitors (at least minimal improvement; follow-up 10 to 24 weeks; measured with: CIBIC+ or ADCS-CGIC; higher is better)									
3[1–3]	RCT	not serious	not serious	not serious	not serious	294/688 (42.7%)	119/347 (34.3%)	RR 1.24 (1.05 to 1.47) 82 more per 1000 (from 17 more to 161 more)	⊕⊕⊕⊕ HIGH
Global response – donepezil (at least minimal improvement; follow-up 10 to 24 weeks; measured with: CIBIC+; higher is better)									
2[1,2]	RCT	not serious	not serious	not serious	serious[5]	160/359 (44.6%)	70/182 (38.5%)	RR 1.15 (0.92 to 1.42) 58 more per 1000 (from 31 fewer to 162 more)	⊕⊕⊕O MODERATE
Global response – rivastigmine (at least minimal improvement; follow-up 24 weeks; measured with: ADCS-CGIC; higher is better)									
1[3]	RCT	not serious	N/A	not serious	serious[5]	134/329 (40.7%)	49/165 (29.7%)	RR 1.37 (1.05 to 1.79) 110 more per 1000 (from 15 more to 235 more)	⊕⊕⊕O MODERATE
CIBIC+ – donepezil (follow-up 10 to 24 weeks; range of scores: 1-7; lower is better)									
2[1,2]	RCT	not serious	serious[6]	not serious	serious[5]	359	182	MD 0.43 lower (0.93 lower to 0.08 higher)	⊕⊕OO LOW
CGIC – donepezil (follow-up 10 weeks; range of scores: 1-7; lower is better)									
1[4]	RCT	not serious	N/A	not serious	very serious[5,7]	19	19	MD 0.37 lower (0.89 lower to 0.15 higher)	⊕⊕OO LOW
UPDRS (total score) – donepezil (follow-up 10 weeks; range of scores: 0-199; lower is better)									
1[4]	RCT	not serious	N/A	not serious	very serious[5,7,8]	21	20	MD 2.3 lower (15.77 lower to 11.17 higher)	⊕⊕OO LOW
ADCS-CGIC – rivastigmine (follow-up 24 weeks; range of scores: 1-7; lower is better)									
1[3]	RCT	not serious	N/A	not serious	not serious	329	165	MD 0.5 lower (0.77 to 0.23 lower)	⊕⊕⊕⊕ HIGH

[1] Aarsland 2002
[2] Dubois 2012; data for 2 active treatment groups were combined (donepezil 5mg and 10mg). Mean and standard deviation calculated from data reported in paper
[3] Emre 2004
[4] Ravina 2005
[5] At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference
[6] i^2 > 40% between studies
[7] Data from a single very small study
[8]CI cross MID of 7.3 points (Schrag et al., 2006)

PDD – cholinesterase inhibitor vs. placebo: activities of daily living

Quality assessment	No of patients	Effect (95% CI)	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Chl	Placebo		
ADL – cholinesterase inhibitors (follow-up 24 weeks; measured with: ADCS-ADL or DAD; higher is better)									
2[1,2]	RCT	not serious	not serious	not serious	not serious	684	335	SMD 0.18 higher (0.05 to 0.31 higher)	⊕⊕⊕⊕ HIGH
DAD – donepezil (follow-up 24 weeks; range of scores 0-100; higher is better)									
1[1]	RCT	not serious	N/A	not serious	serious[3]	351	170	MD 2.26 higher (0.38 lower to 4.89 higher)	⊕⊕⊕O MODERATE
ADCS-ADL – rivastigmine (follow-up 24 weeks; range of scores: 0-78; higher is better)									
1[2]	RCT	not serious	N/A	not serious	not serious	333	165	MD 2.5 higher (0.43 to 4.57 higher)	⊕⊕⊕⊕ HIGH

[1] Dubois 2012; data for 2 active treatment groups were combined (donepezil 5mg and 10mg). Mean and standard deviation calculated from data reported in paper
[2] Emre 2004
[3] At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference

PDD – rivastigmine patches vs. rivastigmine capsules: activities of daily living

Quality assessment						No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Rivastigmine patches**	**Rivastigmine capsules**	**Mean difference (95% CI)**	
ADCS-ADL (follow-up 24 weeks; range of scores: 0-78; higher is better)									
1[1]	RCT	serious[2]	N/A	not serious	serious[3]	270	273	0.9 lower (2.67 lower to 0.87 higher)	⊕⊕OO LOW
ADCS-ADL (follow-up 76 weeks; range of scores: 0-78; higher is better)									
1[1]	RCT	serious[2]	N/A	not serious	not serious	270	273	3.4 lower (5.84 to 0.96 lower)	⊕⊕⊕O MODERATE

[1] Emre 2014
[2] Open-label study
[3] At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference

PDD – cholinesterase inhibitor vs. placebo: other non-cognitive outcomes

Quality assessment						No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Chl**	**Placebo**	**Mean difference (95% CI)**	
NPI-10 item – cholinesterase inhibitors (follow-up 24 weeks; range of scores: 0-120; lower is better)									
2[1,2]	RCT	not serious[3]	not serious	not serious	not serious	688	336	1.67 lower (3.01 to 0.32 lower)	⊕⊕⊕⊕ HIGH
NPI-10 item – donepezil (follow-up 24 weeks; range of scores: 0-120; lower is better)									
1[1]	RCT	not serious[3]	N/A	not serious	serious[4]	354	170	1.34 lower (3.23 lower to 0.54 higher)	⊕⊕⊕O MODERATE
NPI-10 item – rivastigmine (follow-up 24 weeks; range of scores: 0-120; lower is better)									

1[2]	RCT	not serious	N/A	not serious	not serious	334	166	2.00 lower (3.91 to 0.09 lower)	⊕⊕⊕⊕ HIGH
UPDRS III – donepezil (follow-up 10 weeks; lower is better)									
2[5,6]	RCT	serious[7]	not serious	not serious	serious[4,8]	33	32	1.5 lower (7.87 lower to 4.87 higher)	⊕⊕OO LOW

[1] Dubois 2012; data for 2 active treatment groups were combined (donepezil 5mg and 10mg). Mean and standard deviation calculated from data reported in paper
[2] Emre 2004
[3] Data for this outcome not reported in Aarsland 2002. This represents a very small proportion of the total participants in the analysis, therefore quality assessment not downgraded
[4] At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference
[5] Aarsland 2002
[6] Ravina 2005
[7]Data for this outcome not reported in 2 large RCTs (Dubois 2012 and Emre 2004). Papers stated no significant difference between groups
[8]CI cross MID between 3.25 (Horvath et al., 2015) and 5 points (Schrag et al., 2006)

PDD – rivastigmine patches vs. rivastigmine capsules: other non-cognitive outcomes

Quality assessment						No of patients		Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Rivastigmine patches**	**Rivastigmine capsules**	**Mean difference (95% CI)**	
NPI-10 item (follow-up 24 weeks; range of scores: 0-120; lower is better)									
1[1]	RCT	serious[2]	N/A	not serious	serious[3]	273	273	1.6 higher (0.13 lower to 3.33 higher)	⊕⊕OO LOW
NPI-10 item (follow-up 76 weeks; range of scores: 0-120; lower is better)									
1[1]	RCT	serious[2]	N/A	not serious	not serious	273	273	2.3 lower (4.3 to 0.3 lower)	⊕⊕⊕O MODERATE
UPDRS III (follow-up 76 weeks; lower is better)									
1[1]	RCT	serious[2]	N/A	not serious	not serious[4]	175	183	0 higher (2.04 lower to 2.04 higher)	⊕⊕⊕O MODERATE

[1] Emre 2014
[2] Open-label study
[3] At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference
[4]CI do not cross MID between 3.25 (Horvath et al., 2015) and 5 points (Schrag et al., 2006)