G.7.3.5 Mixed population (PDD or DLB) – cholinesterase inhibitors

PDD/DLB – 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)										
7[1–7]	RCT	not serious	not serious	not serious	not serious	810/1034 (78.3%)	369/525 (70.3%)	RR 1.12 (1.05 to 1.19)	84 more per 1000 (from 35 more to 134 more)	⊕⊕⊕⊕ HIGH
Any adverse events – donepezil (probability of experiencing ≥1; follow-up 10 to 24 weeks; lower is better)										
5[1,2,4,6,7]	RCT	not serious	not serious	not serious	serious[8]	453/613 (73.9%)	196/285 (68.8%)	RR 1.06 (0.97 to 1.16)	41 more per 1000 (from 21 fewer to 110 more)	⊕⊕⊕O MODERATE
Any adverse events – rivastigmine (probability of experiencing ≥1; follow-up 20 to 24 weeks; lower is better)										
2[3,5]	RCT	not serious	not serious	not serious	not serious	357/421 (84.8%)	173/240 (72.1%)	RR 1.19 (1.09 to 1.3)	137 more per 1000 (from 65 more to 216 more)	⊕⊕⊕⊕ HIGH
Serious adverse events – cholinesterase inhibitors (probability of experiencing ≥1; follow-up 12 to 24 weeks; lower is better)										
5[2–6]	RCT	not serious	not serious	not serious	serious[8]	137/999 (13.7%)	63/493 (12.8%)	RR 1.10 (0.83 to 1.45)	13 more per 1000 (from 22 fewer to 58 more)	⊕⊕⊕O MODERATE
Serious adverse events – donepezil (probability of experiencing ≥1; follow-up 12 to 24 weeks; lower is better)										
3[2,4,6]	RCT	not serious	not serious	not serious	serious[8]	80/578 (13.8%)	29/253 (11.5%)	RR 1.23 (0.83 to 1.84)	26 more per 1000 (from 19 fewer to 96 more)	⊕⊕⊕O MODERATE
Serious adverse events – rivastigmine (probability of experiencing ≥1; follow-up 20 to 24 weeks; lower is better)										
2[3,5]	RCT	not serious	not serious	not serious	serious[8]	57/421 (13.5%)	34/240 (14.2%)	RR 0.97 (0.65 to 1.43)	4 fewer per 1000 (from 50 fewer to 61 more)	⊕⊕⊕O MODERATE
Adverse events requiring treatment withdrawal – cholinesterase inhibitors (probability of experiencing; follow-up 10 to 24 weeks; lower is better)										

6[1–6]	RCT	not serious	not serious	not serious	not serious	147/1013 (14.5%)	49/505 (9.7%)	RR 1.50 (1.10 to 2.04)	49 more per 1000 (from 10 more to 101 more)	⊕⊕⊕⊕ HIGH
Adverse events requiring treatment withdrawal – donepezil (probability of experiencing; follow-up 10 to 24 weeks; lower is better)										
4[1,2,4,6]	RCT	not serious	not serious	not serious	serious[8]	78/592 (13.2%)	28/265 (10.6%)	RR 1.25 (0.84 to 1.87)	26 more per 1000 (from 17 fewer to 92 more)	⊕⊕⊕O MODERATE
Adverse events requiring treatment withdrawal – rivastigmine (probability of experiencing; follow-up 20 to 24 weeks; lower is better)										
2[3,5]	RCT	not serious	not serious	not serious	not serious	69/421 (16.4%)	21/240 (8.8%)	RR 1.88 (1.17 to 3.03)	77 more per 1000 (from 15 more to 178 more)	⊕⊕⊕⊕ 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] Ikeda 2015; data for 2 active treatment groups were combined (donepezil 5mg and 10mg)
[5] McKeith 2000
[6] Mori 2012; data for 3 active treatment groups were combined (donepezil 3mg, 5mg and 10mg)
[7] Ravina 2005
[8] At a 95% confidence level, data are consistent with appreciable benefit, appreciable harm or no difference

PDD/DLB – cholinesterase inhibitor vs. placebo: cognitive outcomes

Quality assessment						No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	ChI	Placebo	Mean difference (95% CI)	
MMSE – cholinesterase inhibitors (follow-up 10 to 24 weeks; range of scores: 0-30; higher is better)									
7[1–7]	RCT	not serious	not serious	not serious	not serious	1008	503	1.46 higher (1.11 to 1.82 higher)	⊕⊕⊕⊕ HIGH
MMSE – donepezil (follow-up 10 to 24 weeks; range of scores: 0-30; higher is better)									
5[1,2,4,6,7]	RCT	not serious	not serious	not serious	not serious	614	276	1.68 higher (1.24 to 2.11 higher)	⊕⊕⊕⊕ HIGH
MMSE – rivastigmine (follow-up 20 to 24 weeks; range of scores: 0-30; higher is better)									
2[3,5]	RCT	not serious	not serious	not serious	not serious	394	227	1.04 higher (0.43 to 1.65 higher)	⊕⊕⊕⊕ 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] Ikeda 2015; data for 2 active treatment groups were combined (donepezil 5mg and 10mg)
[5] McKeith 2000
[6] Mori 2012; data for 3 active treatment groups were combined (donepezil 3mg, 5mg and 10mg)
[7] Ravina 2005

PDD/DLB – 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	Chl	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)									
5[1–5]	RCT	not serious	serious[6]	not serious	not serious	798	396	SMD 0.48 lower (0.76 to 0.21 lower)	⊕⊕⊕O MODERATE
Global function – donepezil (follow-up 10 to 24 weeks; measured with: CIBIC+, ADCS-CGIC or CGIC; range of scores: 1-7; lower is better)									
4[1,2,3,5]	RCT	not serious	serious[6]	not serious	not serious	469	231	SMD 0.6 lower (1.08 to 0.11 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)									
4[1–4]	RCT	not serious	not serious	not serious	not serious	356/779 (45.7%)	129/377 (34.2%)	RR 1.31 (1.12 to 1.54) 106 more per 1000 (from 41 more to 185 more)	⊕⊕⊕⊕ HIGH
Global response – donepezil (at least minimal improvement; follow-up 10 to 24 weeks; measured with: CIBIC+ or ADCS-CGIC; higher is better)									
3[1,2,4]	RCT	not serious	serious[6]	not serious	not serious	222/450 (49.3%)	80/212 (37.7%)	RR 1.27 (1.04 to 1.55) 102 more per 1000 (from 15 more to 208 more)	⊕⊕⊕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] *Mori 2012; data for 3 active treatment groups were combined (donepezil 3mg, 5mg and 10mg)*
[5] *Ravina 2005*
[6] *Heterogeneity >40% between studies*

PDD/DLB – 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 12 to 24 weeks; range of scores: 0-120; lower is better)[1]									
5[2–6]	RCT	not serious[7]	not serious	not serious	not serious	931	465	1.49 lower (2.69 to 0.29 lower)	⊕⊕⊕⊕ HIGH
NPI-10 item – donepezil (follow-up 12 to 24 weeks; range of scores: 0-120; lower is better)[1]									
3[2,4,6]	RCT	not serious[7]	serious[8]	not serious	serious[9]	550	246	0.92 lower (2.54 lower to 0.69 higher)	⊕⊕OO LOW
NPI-10 item – rivastigmine (follow-up 20 to 24 weeks; range of scores: 0-120; lower is better)									
2[3,5]	RCT	not serious	not serious	not serious	not serious	381	219	2.2 lower (4 to 0.39 lower)	⊕⊕⊕⊕ HIGH
UPDRS III – donepezil (follow-up 24 weeks; lower is better)									
4[4,6,10,11]	RCT	serious[12]	not serious	not serious	not serious[13]	228	109	0.71 lower (2.09 lower to 0.66 higher)	⊕⊕⊕O MODERATE

[1] SD not reported for this outcome in Ikeda 2015; calculated from SE reported in paper
[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] Ikeda 2015; data for 2 active treatment groups were combined (donepezil 5mg and 10mg)
[5] McKeith 2000
[6] Mori 2012; data for 3 active treatment groups were combined (donepezil 3mg, 5mg and 10mg)
[7] 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
[8] Heterogeneity > 40% between studies
[9] At a 95% confidence level, data are consistent with appreciable benefit, appreciable harm or no difference
[10] Aarsland 2002
[11] Ravina 2005
[12]Data for outcome not reported in 3 large RCTs (Dubois 2012, Emre 2004 and McKeith 2000). Papers stated no significant difference between groups
[13]CI do not cross the MID between 3.25 (Horvath et al., 2015) and 5 points (Schrag et al., 2006)