G.7.3.6 Mixed population (PDD or DLB) – memantine

PDD/DLB – memantine vs. placebo: adverse events

Quality assessment						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Memantine	Placebo	Relative (95% CI)	Absolute (95% CI)	
Any adverse events (probability of experiencing ≥1; follow-up 16 to 24 weeks; lower is better)										
2[1,2]	RCT	not serious	not serious	not serious	serious[3]	52/107 (48.6%)	52/113 (46%)	RR 1.06 (0.8 to 1.41)	28 more per 1000 (from 92 fewer to 189 more)	⊕⊕⊕O MODERATE
Serious adverse events (probability of experiencing ≥1; follow-up 16 to 24 weeks; lower is better)										
2[1,2]	RCT	not serious	not serious	not serious	serious[3]	15/107 (14%)	11/113 (9.7%)	RR 1.43 (0.69 to 2.97)	42 more per 1000 (from 30 fewer to 192 more)	⊕⊕⊕O MODERATE
Adverse events requiring treatment withdrawal (probability of experiencing; follow-up 16 to 24 weeks; lower is better)										
2[2,4]	RCT	not serious	not serious	serious[5]	serious[3]	18/130 (13.8%)	21/137 (15.3%)	RR 0.91 (0.51 to 1.63)	14 fewer per 1000 (from 75 fewer to 97 more)	⊕⊕OO LOW

[1] Emre 2010; data reported for total population (PDD and DLB)
[2] Leroi 2009; not clear if adverse event data reported at end of active treatment (16 weeks) or end of drug withdrawal phase (22 weeks)
[3] At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference
[4] Aarsland 2009
[5] Both studies included people who were also taking a cholinesterase inhibitor

PDD/DLB – memantine vs. placebo: cognitive outcomes

Quality assessment						No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Memantine	Placebo	Mean difference (95% CI)	
MMSE (follow-up 16 to 24 weeks; range of scores: 0-30; higher is better)									
2[1,2]	RCT	not serious	not serious	serious[3]	serious[3]	40	47	1.56 higher (0.17 lower to 3.28 higher)	⊕⊕OO LOW

[1] Aarsland 2009
[2] Leroi 2009; data reported for end of drug treatment phase (16 weeks)
[3] Both studies included people who were also taking a cholinesterase inhibitor
[4] At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference

PDD/DLB – memantine vs. placebo: global assessment

Quality assessment						No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Memantine	Placebo	Standardised mean difference (95% CI)	
Global function (follow-up 24 weeks; measured with: ADCS-CGIC or CGIC; range of scores: 1-7; lower is better)									
2[1,2]	RCT	not serious	not serious	not serious	not serious	123	130	0.27 lower (0.51 to 0.02 lower)	⊕⊕⊕⊕ HIGH

[1] Aarsland 2009
[2] Emre 2010; data reported for total population (PDD and DLB)

PDD/DLB – memantine vs. placebo: activities of daily living

Quality assessment						No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Memantine	Placebo	Standardised mean difference (95% CI)	
ADL (follow-up 24 weeks; measured with: ADCS-ADL or DAD; higher is better)									
2[1,2]	RCT	not serious	not serious	not serious	serious[3]	123	130	0.13 higher (0.12 lower to 0.38 higher)	⊕⊕⊕O MODERATE

[1] Aarsland 2009
[2] Emre 2010; data reported for total population (PDD and DLB)
[3] At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference

PDD/DLB – memantine vs. placebo: carer-reported outcomes

Quality assessment						No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Memantine	Placebo	Mean difference (95% CI)	
ZBI (follow-up 16 to 24 weeks; lower is better)									
2[1,2]	RCT	not serious	not serious	not serious	serious[3]	104	111	2.69 lower (5.99 lower to 0.6 higher)	⊕⊕⊕O MODERATE

[1] *Emre 2010; data reported for total population (PDD and DLB)*
[2] *Leroi 2009; data reported for end of drug treatment phase (16 weeks)*
[3] *At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference*

PDD/DLB – memantine vs. placebo: other non-cognitive outcomes

Quality assessment						No of patients		Effect (95% CI)	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Memantine	Placebo		
NPI (follow-up 16 to 24 weeks; measured with: NPI-10 item or NPI 12-item; lower is better)[1]									
2[2,3]	RCT	not serious	not serious	not serious	serious[4]	122	130	SMD 0.16 lower (0.41 lower to 0.08 higher)	⊕⊕⊕O MODERATE
UPDRS III (follow-up 16 to 24 weeks; lower is better)									
2[2,3]	RCT	not serious	not serious	not serious	not serious[5]	131	141	MD 0.28 higher (1.28 lower to 1.85 higher)	⊕⊕⊕⊕ HIGH

[1] *Data from Leroi 2009 could not be included in this analysis due to inconsistent outcome reporting*
[2] *Aarsland 2009*
[3] *Emre 2010; data reported for total population (PDD and DLB)*
[4] *At a 95% confidence level, data are consistent with appreciable harm, appreciable benefit or no difference*
[5] *CI do not cross the MID between 3 (Horvath et al., 2015) and 5 points (Schrag et al., 2006)*

Network meta-analyses

Any adverse events

Quality assessment					Quality
Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	
Adverse events					
9 Aarsland 2002, Dubois 2012, Ikeda 2015, Mori 2012, Ravina 2005, Emre 2004, McKeith 2000, Emre 2010, Leroi 2009	Not serious	Not serious	Not serious[1]	Not serious	High

1. Considered not serious as population, interventions, comparator and outcomes are as defined in protocol

Serious adverse events

Quality assessment					Quality
Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	
Serious adverse events					

Quality assessment					
Number of RCTs	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
7 Dubois 2012, Ikeda 2015, Mori 2012, Emre 2004, McKeith 2000, Emre 2010, Leroi 2009	Not serious	Not serious	Not serious[1]	Not serious	High

1. Considered not serious as population, interventions, comparator and outcomes are as defined in protocol

Adverse events requiring treatment withdrawal

Quality assessment					
Number of RCTs	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
Adverse events requiring treatment withdrawal					
8 Aarsland 2002, Dubois 2012, Ikeda 2015, Mori 2012, Emre 2004, McKeith 2000, Aarsland 2009, Emre 2010	Not serious	Not serious	Not serious[1]	Not serious	High

1. Considered not serious as population, interventions, comparator and outcomes are as defined in protocol

MMSE

Quality assessment					
Number of RCTs	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
Change in MMSE scores					
9 Aarsland 2002, Dubois 2012, Ikeda 2015, Mori 2012, Ravina 2005, Emre 2004, McKeith 2000, Aarsland 2009, Emre 2010	Not serious	Not serious	Not serious[1]	Not serious	High

1. Considered not serious as population, interventions, comparator and outcomes are as defined in protocol

Clincial global function

Quality assessment					
Number of RCTs	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
Change in clinical global function (various measures)					

Quality assessment					
Number of RCTs	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
7 Aarsland 2002, Dubois 2012, Mori 2012, Ravina 2005, Emre 2004, Aarsland 2009, Emre 2010	Not serious	Serious[1]	Not serious[2]	Not serious	Moderate

1. Considerable between study heterogeneity (i^2>40%)
2. Considered not serious as population, interventions, comparator and outcomes are as defined in protocol

NPI

Quality assessment					
Number of RCTs	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
Change in NPI scores					
8 Dubois 2012, Ikeda 2015, Mori 2012, Emre 2004, McKeith 2000, Aarsland 2009, Emre 2010, Leroi 2009	Not serious	Not serious	Not serious[1]	Not serious	High

1. Considered not serious as population, interventions, comparator and outcomes are as defined in protocol

UPDRS III (motor subscale)

Quality assessment					
Number of RCTs	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
Change in UPDRS III (motor) scores					
7 Aarsland 2002, Ikeda 2015, Mori 2012, Ravina 2005, Aarsland 2009, Emre 2010, Leroi 2009	Serious[1]	Not serious	Not serious[2]	Serious[3]	Low

1. Some studies do not report measure of variation
2. Considered not serious as population, interventions, comparator and outcomes are as defined in protocol
3. Analysis could not differentiate between any clinically distinct options