

## G.7.2 Cholinesterase inhibitors and memantine in Alzheimer's disease

- How effective is the co-prescription of cholinesterase inhibitors and memantine for the treatment of Alzheimer's disease?
- When should treatment with donepezil, galantamine, rivastigmine, memantine be withdrawn for people with Alzheimer's disease?

### G.7.2.1 Any cholinesterase inhibitor plus memantine versus any cholinesterase inhibitor plus placebo

#### Full population

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Combination therapy	AChEI monotherapy	Effect size (95% CI)	
<b>Cognition: (ADAS-cog) lower values favour intervention</b>									
Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious <sup>2</sup>	356	353	MD -0.63 (-2.13, 0.87)	Moderate
<b>Cognition: (MMSE) higher values favour intervention</b>									
Dysken 2014; Howard 2012 <sup>a</sup> Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious <sup>2</sup>	410	392	MD 0.14 (-0.47, 0.75)	Moderate
<b>Activities of daily living (ADCS-ADL/BADLS) higher values favour intervention</b>									
Grossberg 2013; Howard 2012 <sup>a</sup> ; Tariot 2004; Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Not serious	943	932	SMD 0.10 (0.01, 0.19)	High
<b>Global functioning (CIBIC plus) lower values favour intervention</b>									
Grossberg 2013; Tariot 2004; Porsteinsson 2008	RCT	Not serious	Not serious	Serious <sup>1</sup>	Not serious	745	738	MD -0.20 (-0.36, -0.04)	Moderate
<b>Behavioural and psychological symptoms (NPI) lower values favour intervention</b>									
Grossberg 2013; Howard 2012 <sup>a</sup> ; Tariot	RCT	Not serious	Not serious	Not serious	Not serious	923	913	MD -1.91 (-3.16, -0.65)	High

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Combination therapy	AChEI monotherapy	Effect size (95% CI)	
2004; Dysken 2014; Porsteinsson 2008									
<b>Care dependency (Behaviour rating scale for geriatric patients- care dependency subscale) lower values favour intervention</b>									
Tariot 2004	RCT	Not serious	Not serious	N/A	Not serious	185	179	MD -1.50 (-2.54, -0.46)	High
<b>Severe impairment battery (SIB)</b>									
Grossberg 2013; Tariot 2004	RCT	Not serious	Not serious	Serious <sup>1</sup>	Serious <sup>2</sup>	530	523	MD 1.22 (-1.15, 3.59)	Low
<b>Verbal fluency test (VFT) higher values favour intervention</b>									
Grossberg 2013		Not serious	Not serious	N/A	Not serious	330	326	MD 0.60 (0.19, 1.01)	High
<b>Health related quality of life (DEMQOL) higher values favour intervention</b>									
Howard 2012 <sup>a</sup>	RCT	Not serious	Not serious	N/A	Serious <sup>2</sup>	58	55	MD -2.00 (-6.44, 2.44)	Moderate
<b>Global health questionnaire (GHQ) higher values favour intervention</b>									
Howard 2012 <sup>a</sup>	RCT	Not serious	Not serious	N/A	Serious <sup>2</sup>	54	45	MD 0.13 (-0.87, 1.13)	Moderate
<b>Total number of adverse events: lower values favour intervention</b>									
Grossberg 2013; Tariot 2004 Dysken 2014 <sup>b</sup>	RCT	Not serious	Not serious	Not serious	Not serious	698	688	RR 1.00 (0.93, 1.09)	High
<b>Number of serious adverse events: lower values favour intervention</b>									
Grossberg 2013; Howard 2012; Dysken 2014 <sup>b</sup> Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious <sup>3</sup>	789	766	RR 0.95 (0.76, 1.19)	Moderate
<b>Number of discontinuations to adverse events: lower values favour intervention</b>									
Grossberg 2013;	RCT	Not serious	Not serious	Serious <sup>1</sup>	Very serious <sup>4</sup>	760	752	RR 0.92 (0.49, 1.71)	Low

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Combination therapy	AChEI monotherapy	Effect size (95% CI)	
Tariot 2004; Porsteinsson 2008									
<b>Mortality: lower values favour intervention</b>									
Grossberg 2013; Howard 2012; Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious <sup>3</sup>	789	776	RR 1.14 (0.80, 1.62)	Moderate
<b>Caregiver activity survey (CAS): higher values favour intervention</b>									
Dysken 2014	RCT	Not serious	Not serious	N/A	Serious <sup>2</sup>	142	140	MD 0.38 (-1.80, 2.56)	Moderate
<b>Entry to care home: lower numbers favour intervention</b>									
Howard 2012	RCT	Not serious	Not serious	N/A	Serious <sup>2</sup>	73	73	HR 1.22 (0.78, 1.90)	Moderate
1. I <sup>2</sup> >40% 2. Non-significant result 3. 95% CI crosses one line of a defined MID interval 4. 95% CI crosses two lines of a defined MID interval a: extracted from additional data (see appendix E) b: Number of adverse events authors attributed to study medication									

### Mild to moderate

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Combination therapy	AChEI monotherapy	Effect size (95% CI)	
<b>Cognition: (ADAS-cog) lower values favour intervention</b>									
Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious <sup>1</sup>	356	353	MD -0.63 (-2.13, 0.87)	Moderate

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Combination therapy	AChEI monotherapy	Effect size (95% CI)	
<b>Cognition: (MMSE) higher values favour intervention</b>									
Dysken 2014; Howard 2012 <sup>a</sup>	RCT	Not serious	Not serious	Not serious	Serious <sup>1</sup>	352	338	MD 0.11 (-0.57, 0.78)	Moderate
<b>Activities of daily living (ADCS-ADL/BADLS) higher values favour intervention</b>									
Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious <sup>2</sup>	356	353	SMD 0.05 (-0.10, 0.20)	Moderate
<b>Global functioning (CIBIC plus) lower values favour intervention</b>									
Porsteinsson 2008	RCT	Not serious	Not serious	N/A	Serious <sup>1</sup>	214	213	MD -0.04 (-0.23, 0.15)	Moderate
<b>Behavioural and psychological symptoms (NPI) lower values favour intervention</b>									
Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious <sup>1</sup>	354	349	MD -0.04 (-2.01, 1.92)	Moderate
<b>Health related quality of life (DEMQOL) higher values favour intervention</b>									
Howard 2012 <sup>a</sup>	RCT	Not serious	Not serious	N/A	Serious <sup>1</sup>	58	55	MD -2.00 (-6.44, 2.44)	Moderate
<b>Total number of adverse events: lower values favour intervention</b>									
Dysken 2014 <sup>b</sup>	RCT	Not serious	Not serious	N/A	Very serious <sup>3</sup>	155	152	RR 1.18 (0.72, 1.94)	Low
<b>Number of serious adverse events: lower values favour intervention</b>									
Dysken 2014 <sup>b</sup> Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Very serious <sup>3</sup>	372	368	RR 0.91 (0.62, 1.33)	Low
<b>Number of discontinuations to adverse events: lower values favour intervention</b>									
Porsteinsson 2008	RCT	Not serious	Not serious	N/A	Very serious <sup>3</sup>	217	216	RR 0.76 (0.38, 1.53)	Low
<b>Mortality: lower values favour intervention</b>									
Dysken 2014;	RCT	Not serious	Not serious	Not serious	Serious <sup>2</sup>	372	368	RR 1.25 (0.83, 1.87)	Moderate

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Combination therapy	AChEI monotherapy	Effect size (95% CI)	
Porsteinsson 2008									
<b>Caregiver activity survey (CAS) higher values favour intervention</b>									
Dysken 2014	RCT	Not serious	Not serious	N/A	Serious <sup>1</sup>	142	140	MD 0.38 (-1.80, 2.56)	Moderate
1. Non-significant result 2. 95% CI crosses one line of a defined MID interval 3. 95% CI crosses two lines of a defined MID interval a: extracted from additional data (see appendix E) b: Number of adverse events authors attributed to study medication									

### Moderate to severe

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Combination therapy	AChEI monotherapy	Effect size (95% CI)	
<b>Cognition: (MMSE) higher values favour intervention</b>									
Howard 2012 <sup>a</sup>	RCT	Not serious	Not serious	N/A	Serious <sup>2</sup>	58	54	MD 0.27 (-1.13, 1.67)	Moderate
<b>Activities of daily living (ADCS-ADL/BADLS) higher values favour intervention</b>									
Grossberg 2013; Howard 2012 <sup>a</sup> ; Tariot 2004	RCT	Not serious	Not serious	Not serious	Serious <sup>3</sup>	587	579	SMD 0.13 (0.01, 0.24)	Moderate
<b>Global functioning (CIBIC plus) lower values favour intervention</b>									
Grossberg 2013; Tariot 2004	RCT	Not serious	Not serious	Serious <sup>1</sup>	Not serious	531	525	MD -0.28 (-0.41, -0.14)	Moderate
<b>Behavioural and psychological symptoms (NPI) lower values favour intervention</b>									

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Combination therapy	AChEI monotherapy	Effect size (95% CI)	
Grossberg 2013; Howard 2012 <sup>a</sup> ; Tariot 2004	RCT	Not serious	Not serious	Not serious	Not serious	569	564	MD -3.19 (-4.83, -1.56)	High
<b>Care dependency (Behaviour rating scale for geriatric patients- care dependency subscale) lower values favour intervention</b>									
Tariot 2004	RCT	Not serious	Not serious	N/A	Not serious	185	179	MD -1.50 (-2.54, -0.46)	High
<b>Severe impairment battery (SIB): higher values favour intervention</b>									
Grossberg 2013; Tariot 2004	RCT	Not serious	Not serious	Serious <sup>1</sup>	Serious <sup>2</sup>	530	523	MD 1.22 (-1.15, 3.59)	Low
<b>Verbal fluency test (VFT) higher values favour intervention</b>									
Grossberg 2013		Not serious	Not serious	N/A	Not serious	330	326	MD 0.60 (0.19, 1.01)	High
<b>Health related quality of life (DEMQOL) higher values favour intervention</b>									
Howard 2012 <sup>a</sup>	RCT	Not serious	Not serious	N/A	Serious <sup>2</sup>	58	55	MD -2.00 (-6.44, 2.44)	Moderate
<b>Global health questionnaire (GHQ) higher values favour intervention</b>									
Howard 2012 <sup>a</sup>	RCT	Not serious	Not serious	N/A	Serious <sup>2</sup>	54	45	MD 0.13 (-0.87, 1.13)	Moderate
<b>Total number of adverse events: lower values favour intervention</b>									
Grossberg 2013; Tariot 2004	RCT	Not serious	Not serious	Not serious	Not serious	372	370	RR 0.99 (0.92, 1.08)	High
<b>Number of serious adverse events: lower values favour intervention</b>									
Grossberg 2013; Howard 2012;	RCT	Not serious	Not serious	Serious <sup>1</sup>	Very serious <sup>4</sup>	417	408	RR 0.98 (0.76, 1.28)	Very low
<b>Number of discontinuations to adverse events: lower values favour intervention</b>									
Grossberg 2013; Tariot 2004; Porsteinsson 2008	RCT	Not serious	Not serious	Serious <sup>1</sup>	Very serious <sup>4</sup>	543	536	RR 0.99 (0.38, 2.58)	Very low

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Combination therapy	AChEI monotherapy	Effect size (95% CI)	
<b>Mortality: lower values favour intervention</b>									
Grossberg 2013; Howard 2012;	RCT	Not serious	Not serious	Not serious	Very serious <sup>4</sup>	417	408	RR 0.90 (0.45, 1.80)	Low
1. $I^2 > 40\%$ 2. Non-significant result 3. 95% CI crosses one line of a defined MID interval 4. 95% CI crosses two lines of a defined MID interval a: extracted from additional data (see appendix E)									

### Mild only

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Combination therapy	AChEI monotherapy	Effect size (95% CI)	
<b>Clinical Global: post-hoc within-trial subgroup analyses (lower values favour intervention)</b>									
Porsteinsson 2008	RCT	Not serious	Not serious	N/A	Very serious <sup>2</sup>	57	64	SMD -0.09 (-0.45, 0.26)	Low
<b>Cognitive Function: post-hoc within-trial subgroup analyses (lower values favour intervention)</b>									
Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious <sup>1</sup>	162	153	SMD -0.05 (-0.27, 0.17)	Moderate
<b>Decline in Activities of Daily Living: post-hoc within-trial subgroup analyses (lower values favour intervention)</b>									
Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious <sup>1</sup>	162	153	SMD -0.04 (-0.26, 0.19)	Moderate
1. 95% CI crosses one line of a defined MID interval 2. 95% CI crosses two lines of a defined MID interval a: extracted from additional data (see appendix E)									

**Moderate only**

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Combination therapy	AChEI monotherapy	Effect size (95% CI)	
<b>Clinical Global: post-hoc within-trial subgroup analyses (lower values favour intervention)</b>									
Porsteinsson 2008; Tariot 2004	RCT	Not serious	Not serious	Serious <sup>1</sup>	Serious <sup>2</sup>	294	312	SMD -0.17 (-0.35, 0.00)	Low
<b>Cognitive Function: post-hoc within-trial subgroup analyses (lower values favour intervention)</b>									
Dysken 2014; Howard 2012; Porsteinsson 2008 Tariot 2004	RCT	Not serious	Not serious	Not serious	Serious <sup>2</sup>	319	338	SMD -0.23 (-0.39, -0.08)	Moderate
<b>Decline in Activities of Daily Living: post-hoc within-trial subgroup analyses (lower values favour intervention)</b>									
Dysken 2014; Howard 2012; Porsteinsson 2008 Tariot 2004	RCT	Not serious	Not serious	Not serious	Serious <sup>2</sup>	322	341	SMD -0.04 (-0.26, 0.19)	Moderate
<b>NPI (lower values favour intervention)</b>									
Howard 2012	RCT	Not serious	Not serious	N/A	Serious <sup>3</sup>	27	28	MD 0.47 (-10.43, 11.37)	Moderate
<b>DEMQOL (higher values favour intervention)</b>									
Howard 2012	RCT	Not serious	Not serious	N/A	Serious <sup>3</sup>	27	28	MD -4.45 (-11.34, 2.44)	Moderate
<b>GHQ-12 (higher values favour intervention)</b>									
Howard 2012	RCT	Not serious	Not serious	N/A	Serious <sup>3</sup>	24	28	MD 0.31 (-1.32, 1.94)	Moderate
1. $I^2 > 40\%$ 2. 95% CI crosses one line of a defined MID interval 3. Non-significant result a: extracted from additional data (see appendix E)									



**Severe only**

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Combination therapy	AChEI monotherapy	Effect size (95% CI)	
<b>Clinical Global: post-hoc within-trial subgroup analyses (lower values favour intervention)</b>									
Tariot 2004	RCT	Not serious	Not serious	N/A	Serious <sup>2</sup>	89	72	SMD -0.22 (-0.53, 0.09)	Moderate
<b>Cognitive Function: post-hoc within-trial subgroup analyses (lower values favour intervention)</b>									
Dysken 2014; Howard 2012; Tariot 2004	RCT	Not serious	Not serious	Not serious	Not serious	120	98	SMD -0.57 (-0.84, -0.30)	High
<b>Decline in Activities of Daily Living: post-hoc within-trial subgroup analyses (lower values favour intervention)</b>									
Howard 2012; Tariot 2004	RCT	Not serious	Not serious	Not serious	Serious <sup>2</sup>	120	98	SMD -0.33 (-0.60, -0.06)	Moderate
<b>NPI (lower values favour intervention)</b>									
Howard 2012	RCT	Not serious	Not serious	N/A	Not serious	31	26	MD -10.24 (-20.30, -0.18)	High
<b>DEMQOL (higher values favour intervention)</b>									
Howard 2012	RCT	Not serious	Not serious	N/A	Serious <sup>1</sup>	31	26	MD 0.49 (-6.02, 7.00)	Moderate
<b>GHQ-12 (higher values favour intervention)</b>									
Howard 2012	RCT	Not serious	Not serious	N/A	Serious <sup>1</sup>	30	23	MD -0.10 (-1.32, 1.12)	Moderate
1. Non-significant result 2. 95% CI crosses one line of a defined MID interval a: extracted from additional data (see appendix E)									