G.7.4.4 **Cognitive impairment in people with multiple sclerosis**

Cholinesterase inhibitors versus placebo

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	AChEI	Placebo	Summary of results	
Cognitive outcomes – global cognition									
Selective reminding test (higher values = better score)									
2 (Krupp 2011, Maurer 2012)	RCT	Not serious	Not serious	Not serious	Serious[1]	104	97	MD 0.64 (-0.43, 1.72)	Moderate
Multiple Sclerosis Inventarium Cognition Score (lower values = better score)									

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	AChEI	Placebo	Summary of results	
1 (Maurer 2012)	RCT	Not serious	Not serious	N/A	Serious[1]	43	38	MD -0.86 (-3.17, 1.45)	Moderate
Cognitive outcomes – domain specific									
Paced Auditory Serial Addition Test 3 (higher values = better score)									
1 (Maurer 2012)	RCT	Not serious	Not serious	N/A	Serious[1]	43	38	MD 1.71 (-1.41, 4.83)	Moderate
Paced Auditory Serial Addition Test 2+3 (higher values = better score)									
1 (Krupp 2011)	RCT	Not serious	Not serious	N/A	Serious[1]	91	59	MD 0.30 (-4.08, 4.68)	Moderate
Faces Symbol Test (lower values = better score)									
1 (Maurer 2012)	RCT	Not serious	Not serious	N/A	Serious[1]	43	38	MD 0.14 (-0.36, 0.64)	Moderate
Symbol digit modalities test (higher values = better score)									
2 (Krupp 2011, Maurer 2012)	RCT	Not serious	Not serious	Not serious	Serious[1]	104	97	MD -1.40 (-3.33, 0.53)	Moderate
Depression									
Montgomery-Asberg Depression Rating Scale (lower values = better score)									
1 (Maurer 2012)	RCT	Not serious	Not serious	N/A	Serious[1]	43	38	MD -1.58 (-3.66, 0.50)	Moderate
Adverse events									
Any adverse events (lower values = better score)									
1 (Maurer 2012)	RCT	Not serious	Not serious	N/A	Serious[2]	35/45	27/41	RR 1.18 (0.90, 1.55)	Moderate
Serious adverse events (lower values = better score)									
2 (Krupp 2011, Maurer 2012)	RCT	Not serious	Not serious	Not serious	Very serious[3]	3/106	6/100	RR 0.46 (0.12, 1.70)	Low
Discontinuation due to adverse events (lower values = better score)									
1 (Maurer 2012)	RCT	Not serious	Not serious	N/A	Very serious[3]	8/45	3/41	RR 2.43 (0.69, 8.55)	Low
MS relapse									
1 (Maurer 2012)	RCT	Not serious	Not serious	N/A	Very serious[3]	4/45	6/41	RR 0.61 (0.18, 2.00)	Low

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*

Memantine versus placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Memantine	Placebo	Summary of results	Quality
			Quality assessment			No of patients		Effect estimate	Quality
Cognitive outcomes - domain specific									
Paced Auditory Serial Addition Test (higher values = better score)									
1 (Saint-Paul 2016)	RCT	Not serious	Not serious	N/A	Serious[1]	31	31	MD 0.70 (-6.51, 5.11)	Moderate
Multiple sclerosis progression									
Expanded Disability Status Scale (lower values = better score)									
1 (Saint-Paul 2016)	RCT	Not serious	Not serious	N/A	Serious[1]	34	34	MD -0.47 (-1.08, 0.12)	Moderate
Adverse events									
Any adverse events (lower values = better score)									
1 (Saint-Paul 2016)	RCT	Not serious	Not serious	N/A	Not serious	36/48	8/38	RR 3.56 (1.88, 6.74)	High
Discontinuation due to adverse events (lower values = better score)									
1 (Saint-Paul 2016)	RCT	Not serious	Not serious	N/A	Very serious[2]	8/50	2/43	RR 3.44 (0.77, 15.34)	Low

1. Non-significant result.
2. 95% CI crosses two lines of a defined MID interval

Network-meta analyses

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Active	Placebo	Summary of results	Quality
			Quality assessment			No of patients		Effect estimate	Quality
Cognitive outcomes – domain specific									
Paced Auditory Serial Addition Test (higher values = better score)									
2 (Maurer 2012, Saint-Paul 2016)	RCT	Not serious	Not serious	N/A	Serious[1]	74	69	See appendix H	Moderate
Adverse events									
Any adverse events (lower values = better score)									
2 (Maurer 2012, Saint-Paul 2016)	RCT	Not serious	Not serious	N/A	Not serious	93	79	See appendix H	High
Discontinuation due to adverse events (lower values = better score)									
2 (Maurer 2012, Saint-Paul 2016)	RCT	Not serious	Not serious	N/A	Serious[1]	93	79	See appendix H	Moderate

1. Analysis could not differentiate any treatment groups.