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- When should treatment with donepezil, galantamine, rivastigmine, memantine be withdrawn for people with Alzheimer's disease?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 patie	ents	Effect estimate	
No of studies	Design	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisio n	Combina tion therapy	AChEI monoth erapy	Effect size (95% CI)	Quality
Cognition: (ADAS-co	g) lower va	alues favour ii	ntervention						
Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious ²	356	353	MD -0.63 (-2.13, 0.87)	Moderate
Cognition: (MMSE) h	igher value	es favour inter	vention						
Dysken 2014; Howard 2012 ^a Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious ²	410	392	MD 0.14 (-0.47, 0.75)	Moderate
Activities of daily livi	ng (ADCS-	ADL/BADLS)	higher values	favour interve	ntion				
Grossberg 2013; Howard 2012 ^a ; 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
Global functioning (C	CIBIC plus)	lower values	favour interve	ention					
Grossberg 2013; Tariot 2004; Porsteinsson 2008	RCT	Not serious	Not serious	Serious ¹	Not serious	745	738	MD -0.20 (-0.36, - 0.04)	Moderate
Behavioural and psy	chological	symptoms (N	PI) lower valu	es favour inter	vention				
Grossberg 2013; Howard 2012 ^a ; Tariot	RCT	Not serious	Not serious	Not serious	Not serious	923	913	MD -1.91 (-3.16, - 0.65)	High

[©] NICE 2018. All rights reserved. See Notice of rights.

Quality assessment						No of patie	ents	Effect estimate	
No of studies	Design	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisio n	Combina tion therapy	AChEI monoth erapy	Effect size (95% CI)	Quality
2004; Dysken 2014; Porsteinsson 2008									
Care dependency (E	Behaviour r	ating scale for	geriatric pati	ents- care dep	endency subs	cale) lower v	alues favo	our intervention	
Tariot 2004	RCT	Not serious	Not serious	N/A	Not serious	185	179	MD -1.50 (-2.54, -0.46)	High
Severe impairment	battery (SIE	3)							
Grossberg 2013; Tariot 2004	RCT	Not serious	Not serious	Serious ¹	Serious ²	530	523	MD 1.22 (-1.15, 3.59)	Low
Verbal fluency test ((VFT) highe	r values favou	ır interventior	ı					
Grossberg 2013		Not serious	Not serious	N/A	Not serious	330	326	MD 0.60 (0.19, 1.01)	High
Health related qualit	ty of life (D	EMQOL) highe	er values favo	ur intervention					
Howard 2012 ^a	RCT	Not serious	Not serious	N/A	Serious ²	58	55	MD -2.00 (-6.44, 2.44)	Moderate
Global health quest	ionnaire (G	HQ) higher va	lues favour in	tervention					
Howard 2012 ^a	RCT	Not serious	Not serious	N/A	Serious ²	54	45	MD 0.13 (-0.87, 1.13)	Moderate
Total number of adv	erse event	s: lower value	s favour inter	vention					
Grossberg 2013; Tariot 2004 Dysken 2014 ^b	RCT	Not serious	Not serious	Not serious	Not serious	698	688	RR 1.00 (0.93, 1.09)	High
Number of serious a	adverse eve	ents: lower val	ues favour in	tervention					
Grossberg 2013; Howard 2012; Dysken 2014 ^b Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious ³	789	766	RR 0.95 (0.76, 1.19)	Moderate
Number of discontin	nuations to	adverse even	ts: lower valu	es favour inter	vention				
Grossberg 2013;	RCT	Not serious	Not serious	Serious ¹	Very serious ⁴	760	752	RR 0.92 (0.49, 1.71)	Low

[©] NICE 2018. All rights reserved. See Notice of rights.

Quality assessment						No of pation	ents	Effect estimate	
No of studies	Design	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisio n	Combina tion therapy	AChEI monoth erapy	Effect size (95% CI)	Quality
Tariot 2004;									
Porsteinsson 2008									
Mortality: lower value	ues favour i	intervention							
Grossberg 2013; Howard 2012; Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious ³	789	776	RR 1.14 (0.80, 1.62)	Moderate
Caregiver activity su	urvey (CAS): higher value	es favour inter	vention					
Dysken 2014	RCT	Not serious	Not serious	N/A	Serious ²	142	140	MD 0.38 (-1.80, 2.56)	Moderate
Entry to care home:	lower num	bers favour ir	ntervention						
Howard 2012	RCT	Not serious	Not serious	N/A	Serious ²	73	73	HR 1.22 (0.78, 1.90)	Moderate
1 12 > 100/									

- 1. I²>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	
No of studies	Design	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisio n	Combina tion therapy	AChEI monoth erapy	Effect size (95% CI)	Quality
Cognition: (ADAS-co	g) lower va	alues favour ir	ntervention						
Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious ¹	356	353	MD -0.63 (-2.13, 0.87)	Moderate

[©] NICE 2018. All rights reserved. See Notice of rights.

Quality assessment						No of patie	ents	Effect estimate	
No of studies	Design	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisio n	Combina tion therapy	AChEI monoth erapy	Effect size (95% CI)	Quality
Cognition: (MMSE) I	nigher value	es favour inte	rvention						
Dysken 2014; Howard 2012 ^a	RCT	Not serious	Not serious	Not serious	Serious ¹	352	338	MD 0.11 (-0.57, 0.78)	Moderate
Activities of daily liv	ing (ADCS	-ADL/BADLS)	higher values	favour interve	ntion				
Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious ²	356	353	SMD 0.05 (-0.10, 0.20)	Moderate
Global functioning (CIBIC plus)	lower values	favour interve	ention					
Porsteinsson 2008	RCT	Not serious	Not serious	N/A	Serious ¹	214	213	MD -0.04 (-0.23, 0.15)	Moderate
Behavioural and psy	/chological	symptoms (N	PI) lower valu	ies favour inter	vention				
Dysken 2014; Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Serious ¹	354	349	MD -0.04 (-2.01, 1.92)	Moderate
Health related qualit	y of life (DE	EMQOL) highe	er values favo	ur intervention					
Howard 2012 ^a	RCT	Not serious	Not serious	N/A	Serious ¹	58	55	MD -2.00 (-6.44, 2.44)	Moderate
Total number of adv	erse events	s: lower value	s favour inter	vention					
Dysken 2014 ^b	RCT	Not serious	Not serious	N/A	Very serious ³	155	152	RR 1.18 (0.72, 1.94)	Low
Number of serious a	dverse eve	nts: lower val	ues favour in	tervention					
Dysken 2014 ^b Porsteinsson 2008	RCT	Not serious	Not serious	Not serious	Very serious ³	372	368	RR 0.91 (0.62, 1.33)	Low
Number of discontin	nuations to	adverse even	ts: lower valu	es favour inter	vention				
Porsteinsson 2008	RCT	Not serious	Not serious	N/A	Very serious ³	217	216	RR 0.76 (0.38, 1.53)	Low
Mortality: lower value	ies favour i	ntervention							
Dysken 2014;	RCT	Not serious	Not serious	Not serious	Serious ²	372	368	RR 1.25 (0.83, 1.87)	Moderate

[©] NICE 2018. All rights reserved. See Notice of rights.

Quality assessment						No of patients		Effect estimate	
No of studies	Design	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisio n	Combina tion therapy	AChEI monoth erapy	Effect size (95% CI)	Quality
Porsteinsson 2008									
Caregiver activity su	rvey (CAS)	higher values	favour interv	vention					
Dysken 2014	RCT	Not serious	Not serious	N/A	Serious ¹	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

loaciate to severe									
Quality assessment						No of patie	ents	Effect estimate	
No of studies	Design	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisio n	Combina tion therapy	AChEI monoth erapy	Effect size (95% CI)	Quality
Cognition: (MMSE) h	igher value	es favour inter	rvention						
Howard 2012 ^a	RCT	Not serious	Not serious	N/A	Serious ²	58	54	MD 0.27 (-1.13, 1.67)	Moderate
Activities of daily livi	ng (ADCS-	ADL/BADLS)	higher values	favour interve	ntion				
Grossberg 2013; Howard 2012 ^a ; Tariot 2004	RCT	Not serious	Not serious	Not serious	Serious ³	587	579	SMD 0.13 (0.01, 0.24)	Moderate
Global functioning (C	IBIC plus)	lower values	favour interve	ention					
Grossberg 2013; Tariot 2004	RCT	Not serious	Not serious	Serious ¹	Not serious	531	525	MD -0.28 (-0.41, - 0.14)	Moderate
Behavioural and psy	chological	symptoms (N	PI) lower valu	es favour inter	vention				

Quality assessment						No of patie	ents	Effect estimate	
No of studies	Design	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisio n	Combina tion therapy	AChEI monoth erapy	Effect size (95% CI)	Quality
Grossberg 2013; Howard 2012 ^a ; Tariot 2004	RCT	Not serious	Not serious	Not serious	Not serious	569	564	MD -3.19 (-4.83, - 1.56)	High
Care dependency (Be	ehaviour ra	ating scale for	geriatric pati	ents- care depe	endency subs	cale) lower v	values favo	ur intervention	
Tariot 2004	RCT	Not serious	Not serious	N/A	Not serious	185	179	MD -1.50 (-2.54, -0.46)	High
Severe impairment b	attery (SIB): higher value	es favour inte	rvention					
Grossberg 2013; Tariot 2004	RCT	Not serious	Not serious	Serious ¹	Serious ²	530	523	MD 1.22 (-1.15, 3.59)	Low
Verbal fluency test (\	/FT) highe	r values favou	r intervention						
Grossberg 2013		Not serious	Not serious	N/A	Not serious	330	326	MD 0.60 (0.19, 1.01)	High
Health related quality	of life (DE	EMQOL) highe	r values favoi	ur intervention					
Howard 2012 ^a	RCT	Not serious	Not serious	N/A	Serious ²	58	55	MD -2.00 (-6.44, 2.44)	Moderate
Global health question	onnaire (GI	HQ) higher val	ues favour in	tervention					
Howard 2012 ^a	RCT	Not serious	Not serious	N/A	Serious ²	54	45	MD 0.13 (-0.87, 1.13)	Moderate
Total number of adve	erse events	s: lower value	s favour inter	vention					
Grossberg 2013; Tariot 2004	RCT	Not serious	Not serious	Not serious	Not serious	372	370	RR 0.99 (0.92, 1.08)	High
Number of serious a	dverse eve	nts: lower val	ues favour int	tervention					
Grossberg 2013; Howard 2012;	RCT	Not serious	Not serious	Serious ¹	Very serious ⁴	417	408	RR 0.98 (0.76, 1.28)	Very low
Number of discontin	uations to	adverse event	ts: lower value	es favour inter	vention				
Grossberg 2013; Tariot 2004; Porsteinsson 2008	RCT	Not serious	Not serious	Serious ¹	Very serious ⁴	543	536	RR 0.99 (0.38, 2.58)	Very low

[©] NICE 2018. All rights reserved. See Notice of rights.

Quality assessment						No of patie	ents	Effect estimate	
No of studies	Design	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisio n	Combina tion therapy	AChEI monoth erapy	Effect size (95% CI)	Quality
Mortality: lower value	es favour i	ntervention							
Grossberg 2013; Howard 2012;	RCT	Not serious	Not serious	Not serious	Very serious ⁴	417	408	RR 0.90 (0.45, 1.80)	Low

- 1. I²>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

Risk of			No of patients				
bias esign	Indirectne ss	Inconsisten cy	Imprecisio n	Combina tion therapy	AChEI monoth erapy	Effect size (95% CI)	Quality
within-trial su	ogroup analyses (le	ower values fav	our interventi	on)			
CT Not ser	ious Not serious	N/A	Very serious ²	57	64	SMD -0.09 (-0.45, 0.26)	Low
t-hoc within-tria	al subgroup analys	es (lower value	s favour inter	vention)			
CT Not se	rious Not serious	Not serious	Serious ¹	162	153	SMD -0.05 (-0.27, 0.17)	Moderate
aily Living: pos	st-hoc within-trial s	ubgroup analys	ses (lower val	ues favour ir	ntervention)	
CT Not ser	ious Not serious	Not serious	Serious ¹	162	153	SMD -0.04 (-0.26, 0.19)	Moderate
11	esign c within-trial sul CT Not seri t-hoc within-tria CT Not seri Daily Living: pos CT Not seri	esign ss c within-trial subgroup analyses (Id CT Not serious Not serious t-hoc within-trial subgroup analyse CT Not serious Not serious eaily Living: post-hoc within-trial s	c within-trial subgroup analyses (lower values favor) CT Not serious Not serious N/A t-hoc within-trial subgroup analyses (lower value) CT Not serious Not serious Not serious paily Living: post-hoc within-trial subgroup analyses CT Not serious Not serious Not serious Not serious Not serious Not serious	c within-trial subgroup analyses (lower values favour intervention of the control	c within-trial subgroup analyses (lower values favour intervention) CT Not serious Not serious N/A Very serious² t-hoc within-trial subgroup analyses (lower values favour intervention) CT Not serious Not serious Not serious Serious¹ 162 Paily Living: post-hoc within-trial subgroup analyses (lower values favour intervention) CT Not serious Not serious Serious¹ 162	c within-trial subgroup analyses (lower values favour intervention) CT Not serious Not serious N/A Very 57 64 t-hoc within-trial subgroup analyses (lower values favour intervention) CT Not serious Not serious Not serious Serious¹ 162 153 Paily Living: post-hoc within-trial subgroup analyses (lower values favour intervention) CT Not serious Not serious Serious¹ 162 153	esign ss cy n therapy erapy Effect size (95% CI) c within-trial subgroup analyses (lower values favour intervention) CT Not serious Not serious N/A Very serious ² t-hoc within-trial subgroup analyses (lower values favour intervention) CT Not serious Not serious Not serious Serious ¹ Not serious Not serious Not serious Serious ¹ Paily Living: post-hoc within-trial subgroup analyses (lower values favour intervention) CT Not serious Not serious Not serious Serious ¹

a: extracted from additional data (see appendix E)

[©] NICE 2018. All rights reserved. See Notice of rights.

Moderate only

Quality assessment						No of pation	ents	Effect estimate	
No of studies	Design	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisio n	Combina tion therapy	AChEI monoth erapy	Effect size (95% CI)	Quality
Clinical Global: post	t-hoc within	ı-trial subgrou	p analyses (le	ower values fav	our interventi	ion)			
Porsteinsson 2008; Tariot 2004	RCT	Not serious	Not serious	Serious ¹	Serious ²	294	312	SMD -0.17 (-0.35, 0.00)	Low
Cognitive Function:	post-hoc w	ithin-trial sub	group analys	es (lower value	s favour inter	vention)			
Dysken 2014; Howard 2012; Porsteinsson 2008 Tariot 2004	RCT	Not serious	Not serious	Not serious	Serious ²	319	338	SMD -0.23 (-0.39, - 0.08)	Moderate
Decline in Activities	of Daily Liv	/ing: post-hoc	within-trial s	ubgroup analys	ses (lower val	ues favour i	nterventior	1)	
Dysken 2014; Howard 2012; Porsteinsson 2008 Tariot 2004	RCT	Not serious	Not serious	Not serious	Serious ²	322	341	SMD -0.04 (-0.26, 0.19)	Moderate
NPI (lower values fa	vour interv	ention)							
Howard 2012	RCT	Not serious	Not serious	N/A	Serious ³	27	28	MD 0.47 (-10.43, 11.37)	Moderate
DEMQOL (higher va	lues favour	intervention)							
Howard 2012	RCT	Not serious	Not serious	N/A	Serious ³	27	28	MD -4.45 (-11.34, 2.44)	Moderate
GHQ-12 (higher valu	ies favour i	ntervention)							
Howard 2012 1. I ² >40% 2. 95% CI cross 3. Non-significat a: extracted from	nt result	Not serious of a defined MI		N/A	Serious ³	24	28	MD 0.31 (-1.32, 1.94)	Moderate

[©] NICE 2018. All rights reserved. See Notice of rights.

Severe only

Quality assessme	nt					No of patie	ents	Effect estimate	
No of studies	Design	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisio n	Combina tion therapy	AChEI monoth erapy	Effect size (95% CI)	Quality
Clinical Global: po	ost-hoc within	n-trial subgrou	p analyses (le	ower values fav	our interventi	ion)			
Tariot 2004	RCT	Not serious	Not serious	N/A	Serious ²	89	72	SMD -0.22 (-0.53, 0.09)	Moderate
Cognitive Functio	n: post-hoc v	vithin-trial sub	group analys	es (lower value	s favour inter	vention)			
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
Decline in Activiti	es of Daily Li	ving: post-hoc	within-trial s	ubgroup analy	ses (lower val	ues favour i	nterventio	1)	
Howard 2012; Tariot 2004	RCT	Not serious	Not serious	Not serious	Serious ²	120	98	SMD -0.33 (-0.60, - 0.06)	Moderate
NPI (lower values	favour interv	ention)							
Howard 2012	RCT	Not serious	Not serious	N/A	Not serious	31	26	MD -10.24 (-20.30, - 0.18)	High
DEMQOL (higher	values favou	r intervention)							
Howard 2012	RCT	Not serious	Not serious	N/A	Serious ¹	31	26	MD 0.49 (-6.02, 7.00)	Moderate
GHQ-12 (higher va	alues favour i	intervention)							
Howard 2012	RCT	Not serious	Not serious	N/A	Serious ¹	30	23	MD -0.10 (-1.32, 1.12)	Moderate
 Non-signifi 95% Cl cro 		of a defined MI	D interval						
a: extracted fro	m additional c	lata (see appen	dix E)						