Role of Memantine

Q2: For people with dementia, does memantine, when compared to placebo/comparator, produce benefits/harm in the specified outcomes in non-specialist health settings?

Background

While the issue of whether dementia can be diagnosed by non-specialist health care providers is addressed by a different scoping question, there is agreement that at non-specialist level of care it is not feasible to differentiate the various forms of dementias, including Alzheimer's disease, vascular dementia, Lewy bodies dementia, and other forms of dementia. In this scoping question, therefore, individuals with dementia are the target population. It is anticipated, however, that most randomized controlled trials, and most systematic reviews, were carried out in specific subtypes of dementias. The body of evidence is therefore presented and described following this categorization, and then a draft recommendation has been formulated by generalizing this evidence to the broad category of individuals with dementia.

Population/Intervention(s)/Comparison/Outcome(s) (PICO)

Population:	individuals with dementias, including Alzheimer's disease, vascular dementia, dementia with Lewy bodies
Intervention:	memantine
Comparison:	placebo
Outcomes:	cognitive functioning
	behavioural disturbances
	functional status
	mortality
	adverse effects of interventions

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES

Kavirajan H, Schneider LS (2007). Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomized controlled trials. *Lancet Neurology,* 6:782–92.

McShane R, Areosa Sastre A, Minakaran N (2006). Memantine for dementia. *Cochrane Database of Systematic Reviews,* (2):CD003154.

PICO table

Serial no.	Intervention/Comparison	Outcomes	Included Reviews	Explanation
4	**Memantine vs. Placebo**	- Cognitive functioning - Behavioural disturbances - Functional status - Mortality - Adverse effects of interventions - Global status	McShane R, Areosa Sastre A, Minakaran N (2006). Memantine for dementia. *Cochrane Database of Systematic Reviews,* (2):CD003154. Kavirajan H, Schneider LS (2007). Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomized controlled trials. *Lancet Neurology,* 6: 782–92.	Recent systematic reviews relevant to the area

Narrative description of the studies that went into the analysis

The review carried out by McShane et al, 2006 included twelve trials. They studied the efficacy and tolerability of various dosages of memantine in different types of dementia and at different stages of the disease. All included trials were of parallel-group design. There were nine phase III studies that lasted between 12 and 28 weeks; The other three included studies were phase II trials that lasted four or six weeks. The number of participants ranged from 60 to 579. Two studies involved only people with vascular dementia defined by the National Institute of Neurological Disorders and Stroke and the Association International pour la Recherche et l'Enseignement en Neurosciences. Six studies were restricted to people with Alzheimer's disease diagnosed according to the criteria of the National Institute of Neurologic, Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association. Three studies included both types of dementia in various proportions. In these studies, the Hachinski score was used to differentiate between Alzheimer's disease and vascular dementia. In one trial there is no record of an attempt to distinguish different types of dementia.

GRADE tables

Table 1

Author(s): T Dua, C Barbui
Date: 2009-06-07
Question: Should memantine vs. placebo be used for moderate-to-severe Alzheimer's disease?
Settings:
Bibliography: McShane R, Areosa Sastre A, Minakaran N (2006). Memantine for dementia. *Cochrane Database of Systematic Reviews,* (2):CD003154.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	memantine	placebo	Relative (95% CI)	Absolute		
Cognitive function - SIB (Better indicated by higher values)												

3[1]	randomized trials	no serious limitations	serious[2]	no serious indirectness	no serious imprecision	none	492	484	-	MD 2.97 higher (1.68 to 4.26 higher)	MODERATE	IMPORTANT
Cognitive function - MMSE (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Global assessment (Better indicated by higher values)												
3[3]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	487	477	-	MD 0.28 higher (0.15 to 0.41 higher)	HIGH	IMPORTANT
Behavioural disturbances (Better indicated by higher values)												
3[4]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[5]	none	474	462	-	MD 2.76 higher (0.88 to 4.63 higher)	MODERATE	CRITICAL
Functional status (activities of daily living) (Better indicated by higher values)												
3[6]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	493	485	-	MD 1.27 higher (0.44 to 2.09 higher)	HIGH	CRITICAL
Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Treatment acceptability (total dropouts)												
3[7]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	103/507 (20.3%)	139/499 (27.9%)	OR 0.66 (0.49 to 0.88)	75 fewer per 1000 (from 25 fewer to 119 fewer)	HIGH	CRITICAL
Treatment acceptability (dropouts due to adverse events)												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
Adverse events												

3[8]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	395/506 (78.1%)	379/499 (76%)	OR 1.13 (0.84 to 1.52)	22 more per 1000 (from 33 fewer to 68 more)	HIGH	CRITICAL

[1] From Analysis 1.2 of McShane et al, 2006 Cochrane Review.
[2] Heterogeneity exceeds 50% (I-squared = 74%).
[3] From Analysis 1.1 of McShane et al, 2006 Cochrane Review.
[4] From Analysis 1.4 of McShane et al, 2006 Cochrane Review.
[5] Confidence interval ranges from appreciable benefit to almost no difference.
[6] From Analysis 1.3 of McShane et al, 2006 Cochrane Review.
[7] From analysis 1.5 of McShane et al, 2006 Cochrane Review.
[8] From Analysis 1.6 of McShane et al, 2006 Cochrane Review.

Table 2

Author(s): T Dua, C Barbui
Date: 2009-06-07
Question: Should memantine vs. placebo be used for mild-to-moderate Alzheimer's disease?
Settings:
Bibliography: McShane R, Areosa Sastre A, Minakaran N (2006). Memantine for dementia. *Cochrane Database of Systematic Reviews,* (2):CD003154.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**memantine**	**placebo**	**Relative (95% CI)**	**Absolute**		
Cognitive function - ADAS-Cog (Better indicated by higher values)												
3[1]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	718	561	-	MD 0.99 higher (0.21 to 1.78 higher)	HIGH	IMPORTANT
Cognitive function - MMSE (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Global assessment (Better indicated by higher values)												

3[2]	randomized trials	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	none	720	561	-	MD 0.13 higher (0.01 to 0.25 higher)	MODERATE	IMPORTANT
Behavioural disturbances (Better indicated by higher values)												
3[4]	randomized trials	no serious limitations	serious[5]	no serious indirectness	serious[6]	none	707	545	-	MD 0.25 lower (1.48 lower to 0.98 higher)	LOW	CRITICAL
Functional status (activities of daily living) (Better indicated by higher values)												
3[7]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[6]	none	714	557	-	MD 0.20 higher (0.87 lower to 1.27 higher)	MODERATE	CRITICAL
Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Treatment acceptability (total dropouts)												
3[8]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	106/736 (14.4%)	74/570 (13%)	RR 1.16 (0.83 to 1.6)	21 more per 1000 (from 22 fewer to 78 more)	HIGH	CRITICAL
Treatment acceptability (dropouts due to adverse events)												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
Adverse events												
3[9]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	493/736 (67%)	397/570 (69.6%)	OR 1.04 (0.81 to 1.33)	8 more per 1000 (from 46 fewer to 57 more)	HIGH	CRITICAL

[1] From Analysis 2.2 of McShane et al, 2006 Cochrane Review.

[2] From Analysis 2.1 of McShane et al, 2006 Cochrane Review.

[3] Analysis of the funnel plot revealed some heterogeneity (I-squared = 48%).

[4] From Analysis 2.4 of McShane et al, 2006 Cochrane Review.

[5] Heterogeneity exceeds 50% (I-squared=66%).

[6] The 95% confidence interval ranges from appreciable benefit to appreciable harm.

[7] From Analysis 2.3 of McShane et al, 2006 Cochrane Review.

[8] From Analysis 2.5 of McShane et al, 2006 Cochrane Review.
[9] From Analysis 2.10 of McShane et al, 2006 Cochrane Review.

Table 3

Author(s): T Dua, C Barbui
Date: 2009-06-07
Question: Should memantine vs. placebo be used for vascular dementia?
Settings:
Bibliography: Kavirajan H, Schneider LS (2007). Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomized controlled trials. *Lancet Neurology,* 6: 782–92.

McShane R, Areosa Sastre A, Minakaran N (2006). Memantine for dementia. *Cochrane Database of Systematic Reviews,* (2):CD003154.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	memantine	placebo	Relative (95% CI)	Absolute		
Cognitive function - ADAS-Cog (Better indicated by higher values)												
2[1]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	413	402	-	MD 1.85 higher (0.88 to 2.83 higher)[2]	HIGH	IMPORTANT
Cognitive function - MMSE (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Number of patients improved (global assessment)												
1[3]	randomized trials	no serious limitations	no serious inconsistency	serious[4]	serious[5]	none	88/147 (59.9%)	74/141 (52.5%)	OR 1.34 (0.85 to 2.15)	72 more per 1000 (from 41 fewer to 179 more)	LOW	IMPORTANT
Behavioural disturbances (Better indicated by higher values)												

2[6]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[7]	none	287	254	-	MD 0.48 higher (0.06 to 0.91 higher)	MODERATE	CRITICAL
Functional status (activities of daily living) (Better indicated by higher values)												
2[8]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[9]	none	285	257	-	MD 0.12 higher (0.43 lower to 0.67 higher)	MODERATE	CRITICAL
Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Treatment acceptability (total dropouts)												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
Treatment acceptability (dropouts due to adverse events)												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
Adverse events												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL

[1] From Analysis 3.2 of McShane et al, 2006 Cochrane Review.

[2] Kavirajan and Schneider, 2007 in their meta-analysis of randomized controlled trials conducted in individuals with vascular dementia identified two trials for memantine, and calculated a mean difference of -1.86 (-2.79 to -0.94).

[3] From Figure 3 of Kavirajan and Schneider, 2007 review.

[4] Only one study was included in this analysis.

[5] Estimate ranges from appreciable benefit to appreciable harm.

[6] From Analysis 3.4 of McShane et al, 2006 Cochrane Review.

[7] The confidence interval ranges from appreciable benefit to almost no difference.

[8] From Analysis 3.3 of McShane et al, 2006 Cochrane Review.

[9] The 95% confidence interval ranges from appreciable benefit to appreciable harm.

Table 4

Author(s): T Dua, C Barbui
Date: 2009-06-07
Question: Should memantine vs. placebo be used for mild-to-severe dementia?
Settings:
Bibliography: McShane R, Areosa Sastre A, Minakaran N (2006). Memantine for dementia. *Cochrane Database of Systematic Reviews,* (2):CD003154.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	memantine	placebo	Relative (95% CI)	Absolute		
Cognitive function (Better indicated by higher values)												
8[1]	randomized trials	no serious limitations	serious[2]	no serious indirectness	no serious imprecision	none	0[3]	0[3]	-	MD 0.24 higher (0.17 to 0.3 higher)	MODERATE	IMPORTANT
Cognitive function - MMSE (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT
Global assessment (Better indicated by higher values)												
8[4]	randomized trials	no serious limitations	no serious inconsistency	serious[5]	no serious imprecision	none	1598	1422	-	MD 0.15 higher (0.07 to 0.23 higher)	MODERATE	IMPORTANT
Behavioural disturbances (Better indicated by higher values)												
8[6]	randomized trials	no serious limitations	serious[7]	no serious indirectness	no serious imprecision	none	304	146	-	SMD 0.11 higher (0.04 to 0.19 higher)	MODERATE	CRITICAL
Functional status (activities of daily living) (Better indicated by higher values)												
8[8]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0[3]	0[3]	-	MD 0.08 higher (0.01 to 0.15 higher)	HIGH	CRITICAL

Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
Treatment acceptability (total dropouts)												
8[9]	randomized trials	no serious limitations	serious[10]	no serious indirectness	no serious imprecision	none	315/1703 (18.5%)	309/1509 (20.5%)	OR 0.91 (0.76 to 1.09)	15 fewer per 1000 (from 41 fewer to 14 more)	MODERATE	CRITICAL
Treatment acceptability (dropouts due to adverse events)												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
Adverse events												
8[11]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1239/1702 (72.8%)	1103/1509 (73.1%)	OR 1.09 (0.93 to 1.27)	17 more per 1000 (from 15 fewer to 44 more)	HIGH	CRITICAL

[1] From Analysis 6.2 of McShane et al, 2006 Cochrane Review.

[2] Some degree of heterogeneity can be detected from the forest plot, even though the I-squared does not exceed 50% (I-squared = 43%).

[3] Absolute numbers not reported.

[4] From Analysis 6.1 of McShane et al, 2006 Cochrane Review.

[5] Different rating scales are pooled together.

[6] From Analysis 6.4 of McShane et al, 2006 Cochrane Review.

[7] Although the I-squared did not detect high level heterogeneity (I-squared = 44%) visual inspection of forest plot suggested some degree of heterogeneity.

[8] From Analysis 6.3 of McShane et al, 2006 Cochrane Review.

[9] From Analysis 6.5 of McShane et al, 2006 Cochrane Review.

[10] Some degree of heterogeneity can be detected from the forest plot, even though the I-squared does not exceed 50% (I-squared = 48%).

[11] From Analysis 6.6 of McShane et al, 2006 Cochrane Review.

Additional information that was not GRADEd (safety and tolerability issues, cost, resource use, and other feasibility issues, if appropriate)

Memantine was originally licensed for moderately severe to severe Alzheimer's disease, but the licence was extended in November 2005 and now covers moderate to severe Alzheimer's disease. Apart from rivastigmine, no drugs are currently licensed for the symptomatic treatment of people with vascular

dementia, dementia with Lewy bodies, or other dementias (subcortical or mixed dementias), although people with these forms of dementia suffer similar problems associated with cognitive symptoms and loss of daily living skills.

Reference List

Kavirajan H, Schneider LS (2007). Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomized controlled trials. *Lancet Neurology,* 6:782–92.

McShane R, Areosa Sastre A, Minakaran N (2006). Memantine for dementia. *Cochrane Database of Systematic Reviews,* (2):CD003154.

From evidence to recommendations

Factor	**Explanation**				
Narrative summary of the evidence base	Outcome	Moderate-to-severe Alzheimer's disease	Mild-to-moderate Alzheimer's disease	Vascular dementia	Dementias
	Cognitive function	3 studies, MD 2.97 (1.68 to 4.26, favouring active treatment)	3 studies, MD 0.99 (0.21 to 1.78, favouring active treatment)	2 studies, MD 1.85 (0.88 to 2.83, favouring active treatment)	8 studies, MD 0.24 (0.17 to 0.30, favouring active treatment)
	Global assessment	3 studies MD 0.28 (0.15 to	3 studies MD 0.13 (0.01 to	1 study OR 1.34 (0.85 to	8 studies MD 0.15 (0.07 to 0.23) favouring active treatment

		0.41) favouring active treatment	0.25) favouring active treatment	2.15) no difference	
	Behavioural disturbances	3 studies MD 2.76 (0.88 to 4.63, favouring active treatment)	3 studies MD -0.25 (-1.48 to 0.98, no difference)	2 studies MD 0.48 (0.06 to 0.91, favouring active treatment)	8 studies SMD 0.11 (0.04 to 0.19, favouring active treatment)
	Functional status	3 studies, MD 1.27 (0.44 to 2.09, favouring active treatment)	3 studies, MD 0.20 (-0.87 to 1.27, no difference)	2 studies, MD 0.12 (-0.43 to 0.67, no difference)	8 studies, MD 0.08 (0.01 to 0.15, favouring active treatment)
	Adverse events	3 studies, OR 1.13 (0.84 to 1.52, no difference)	3 studies, OR 1.04 (0.81 to 1.33, no difference)	-	8 studies, OR 1.09 (0.93 to 1.27, no difference)
Summary of the quality of evidence	Outcome	Moderate-to-severe Alzheimer's disease	Mild-to-moderate Alzheimer's disease	Vascular dementia	Dementias

	Cognitive function	LOW	MODERATE	MODERATE	LOW
	Global assessment	HIGH	MODERATE	LOW	MODERATE
	Behavioural disturbances	MODERATE	LOW	MODERATE	MODERATE
	Functional status	MODERATE	LOW	LOW	MODERATE
	Adverse events	HIGH	HIGH	-	HIGH
Balance of benefits versus harms	Small beneficial effect on the different outcomes for moderate to severe Alzheimer's Disease. With mild to moderate Alzheimer's Disease, there is a smaller although significant effect on cognition barely detectable clinically and no effect on activities of daily living. Memantine was well tolerated. Although cognitive functioning, functional status and behavioural disturbances can be improved with memantine treatment, it is unclear whether improvement observed in clinical trials translates into clinically meaningful beneficial effects in clinical practice.				
Values and preferences including any variability and human rights issues	Cognitive decline and lack of functioning (activities of daily living) seen in people with dementia represents a serious burden for patients and their families. However, safety in the long-term may represent a concern, and adherence to treatment may be particularly problematic in patient population that may require complex treatment regimes. It is also not feasible to differentiate mild from moderate to severe Alzheimer's Disease by non-specialist health care providers.				
Costs and resource use and any other relevant	Most evidence has been collected in Alzheimer's disease, but it is not feasible in non-specialized health care settings to differentiate Alzheimer's disease from other forms of dementia. The body of existing evidence has therefore to be applied to the broad category of individuals with dementia.				

feasibility issues	Additionally, in most health care systems memantine are associated with high acquisition costs. Memantine is not included in the WHO list of essential medicines. Treatment is best initiated and continued with specialist involvement which may not be available. In all cases regular clinical monitoring is required.
Final recommendation Memantine should not be considered routinely for people with dementia in non-specialist health settings in low and middle income countries. Strength of recommendation: STANDARD Memantine may be considered only when diagnosis of moderate to severe Alzheimer's Disease has been made, with adequate support and supervision by specialist. Consideration should be given to adherence and monitoring of adverse effects, which generally requires the availability of a carer. Baseline structured cognitive and functional assessment should be carried out. Follow up should be carried out on regular basis at least 3 monthly and treatment needs to be terminated in case of non-response. Strength of recommendation: STANDARD	
Any additional remarks	

Limitations

The comparative efficacy of memantine versus other drug treatments for patients with dementia has not been reviewed. Additionally, the evidence base may suffer from selective publication of studies in favour of memantine over placebo.

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following systematic reviews were found to be relevant without changing the recommendation:

Lockhart IA, Orme ME, Mitchell SA. The Efficacy of Licensed-Indication Use of Donepezil and Memantine Monotherapies for Treating Behavioural and Psychological Symptoms of Dementia in Patients with Alzheimer's Disease: Systematic Review and Meta-Analysis. Dementia and Geriatric Cognirive Disorder Extra 2011, 1:212-227, DOI: 10.1159/000330032

McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD003154. DOI: 10.1002/14651858. CD003154.pub5.