Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

"In patients with early or mild stage Alzheimer's dementia, how effective is memantine when compared to standard care, in slowing the progression of dementia and/or delaying admittance to institutionalised care.?"

Clarification of question using PICO structure

Patients:	Patients with early or mild stage Alzheimer's dementia
Intervention:	Memantine
Comparator:	Standard care
Outcome:	Slowing the progression of dementia and/or delaying admittance to institutionalised care.

Clinical and research implications

The limited evidence currently available does not support the routine use of memantine to delay disease progression in patients with early or mild stage Alzheimer's dementia.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified two reports of one Cochrane Collaboration systematic review, which met the PICOS criteria for this abstract.[1,2] This review included three un-published double blind placebo-controlled RCTs of memantine, with a total of 1306 participants (1282 included in the analyses).

Additional searches for RCTs identified one aditional article[4], which was a partial report of one of the RCTs included in the systematic review described above and did not provide any additional information relevant to this abstract. The second RCT[3] included 67 participants, of whom 63 completed the study and were included in the analyses and compared memantine with donepezil.

Main findings

All studies included in the systematic review compared memantine (20mg/d) with placebo, with a study duration of six months, and reported clinical outcomes as weighted mean difference (WMD) in change from baseline between groups.

The full report of the Cochrane review[1] indicated that, in patients with mild to moderate Alzheimer's disease, treatment with memantine may reduce decline in cognitive function over six months compared with placebo; WMD for ADAS-Cog = 0.99 (95% CI 0.21 to 1.78). However, differences between memantine and placebo were non-significant or borderline for other outcomes (activities of daily living, clinical global impression, and neurpsychiatric inventory). The publication of one of the RCTs included in the review[4] reported similar results for the cognitive function outcome only and further noted that significant differences were observed for the language and memory sub-scales of the ADAS-Cog only.

The second report of the Cochrane review[2] was of greater relevance to the PICOs criteria for this abstract, since it reported results stratified by severity of Alzheimer's disease (mild and moderate). For patients with mild Alzheimer's disease (Mini Mental State Examination scores 20 to 23), there were no significant differences between memantine and placebo for any of the outcomes measured (cognitive function, activities of daily living, clinical global impression, and neurpsychiatric inventory). For patients with moderate Alzheimer's disease (Mini Mental State Examination scores 10 to 19), results were similar to those for the whole population; memantine was associated with a significant reduction in decline in cognitive function compared with placebo (WMD for ADAS-Cog = –1.33 (95% CI –2.28 to –0.38).

The trial which compared memantine with donepezil found no significant differences in decline from baseline, between treatment groups, for any of the outcomes measured (Alzheimer's Disease Assessment Scale, neuropsychiatric inventory and disability assessment for Dementia).[3]

Authors conclusions

The two reports of the Cochrane systematic review concluded that there is meagre evidence of some small benefit on cognition for patients with mild to moderate[1]/moderate[2] Alzheimer's disease and that evidence is lacking for a benefit of memantine in mild Alzheimer's disease.[2]

The authors of the placebo-controllled RCT of memantine included in the Cochrane review[4] concluded that memantine benefits core aspects of language and some aspects of memory in patients with mild to moderate AD.

The authors of the RCT comparing memantine and donepezil concluded that donepezil and memantine have similar modest clinical effects in patients with mild to moderate Alzheimer's disease.

Reliability of conclusions/Strength of evidence

The systematic review report [2] and additional RCT[3], which were of greatest relevance to this abstract were both rated as 'low' or 'unclear' risk of bias on all criteria.

The limited available evidence suggests that memantine is not clinically effective in patients with mild Alzheimer's disease and may have some small effect in reduction decline in cognition in patients with moderate Alzheimer's disease. However, data specific to the mild Alzheimer's disease population are very sparse (most studies combine data for mild to moderate disease). More trials are needed to provide evidence on the effectiveness of memantine in patients with mild Alzheimer's disease, its effectiveness in comparison with alternative treatments and effectiveness over the longer term (>six months).

What do guidelines say?

The NICE guideline on Dementia (CG42)[5] recommends memantine as an option for managing people with moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors or people with severe Alzheimer's disease.

NICE guidance on donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (NTAG 111)[6] recommends memantine as an option for managing people with moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors or people with severe Alzheimer's disease. The guidance further specifies that memantine should be used only by specialists in the care of patients with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of older people), and that carers' views on the patient's condition at baseline should be sought.

The SIGN guideline on the management of patients with dementia[7] states that there is currently insufficient evidence to recommend the use of memantine for the treatment of core or associated symptoms in people with dementia.

These guidelines are broadly consistent with the evidence summarised in this abstract.

Date question received: 19/08/2011
Date searches conducted: 01/12/2011
Date answer completed: 13/01/2012

References

Systematic Reviews

1. 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.

2. Schneider L, Dagerman k, Higgins J, McShane R. Lack of Evidence for the Efficacy of Memantine in Mild Alzheimer Disease. *Arch Neurol. 2011;68(8):991-998.*

Randomised Controlled Trials

3. Modrego P, Fayed N, Errea J, Rios C, Pina M, Sarasa M. Memantine versus donepezil in mild to moderate Alzheimer's disease: a randomized trial with magnetic resonance spectroscopy. European Journal of Neurology 2010, 17: 405–412.

4. Pomara N, Ott B, Peskind E, Resnick E. Memantine Treatment of Cognitive Symptoms in Mild to Moderate Alzheimer Disease: Secondary Analyses From a Placebo-controlled Randomized Trial. *Alzheimer Dis Assoc Disord*, 2007, 21: Number 1 January–March 2007.

Guidelines

5. National Institute for Health and Clinical Excellence (November2006) NICE clinical guideline 42 (amended March 2011) Dementia: supporting people with dementia and their carers in health and social care. http://www.nice.org.uk/nicemedia/pdf/CG042NICEGuideline.pdf

6. National Institute for Health and Clinical Excellence (March 2004) NICE technology appraisal guidance 217. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of NICE technology appraisal guidance 111) http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf

7. Scottish Intercollegiate Guidelines Network (February 2006) Management of Patients with Dementia, a national clinical guideline. http://www.sign.ac.uk/pdf/sign86.pdf

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
McShane (2009)	Feb 2006	*Participants;* People with Alzheimer's, vascular, mixed or unspecified dementia of all degrees of severity, treated as in- or out-patients. *Interventions;* Treatment with memantine at any dose and by any route of administration in an acceptable clinical trial. *Comparator;* Placebo. *Outcomes;* The primary outcomes of interest were. 1- Clinical Global Impression 2- Cognitive function 3- Functional performance 4- Behavioural disturbance 5- Effect on carers 6- Quality of Life 7- Incidence and severity of adverse effects 8- Institutionalization 9- Costs *Study design;* Double-blind, parallel group, placebo-	3 un-published studies of memantine vs. placebo in mild to moderate AD (n= 1306 randomised).	All three included studies compared memantine (20mg/d) with placebo. The following outcomes were reported as weighted mean difference (WMD), between the memantine and placebo groups, in change from baseline measured at 24 weeks: Memantine was associated with a borderline significant benefit in clinical global outcome (CIBIC+) ; WMD 0.13 (95% CI 0.01 to 0.25), based on data from all 3 RCTs (n=1281). Memantine was associated with a significant benefit in cognitive function outcome (ADAS-Cog); WMD 0.99 (95% CI 0.21 to 1.78), based on data from all 3 RCTs (n=1279). There was no significant difference, between memantine and placebo, in the activities of daily living outcome (ADCS-ADL23) at 24 weeks; WMD 0.20 (95% CI -0.87 to 1.27), based on data from all three RCTs (n=1271). There was no significant difference, between memantine and placebo, in the mood and behaviour outcome (NPI total) at 24 weeks;	This review included only placebo-controlled trials; direct comparisons with other interventions were excluded and this may limit the applicability of the review to the question specified for this abstract. Although the review methods specify the involvement of two reviewers in study selection (minimising

		controlled RCTs.		WMD -0.25 (95% CI -1.48 to 0.98), based on data from all three RCTs (n=1252). Data on drop out rates and adverse events were also reported. All three studies were reported as being double-blind randomised controlled trials. All three studies were rated as unclear with respect to the allocation concealment item of the risk of bias assessment (no details of allocation concealment were reported).	the potential for error and/or bias), it is not clear whether two reviewers were involved throughout the review process (data extraction and quality assessment). Pooled estimates of clinical effectiveness (particularly the use of a fixed effects model) are of questionable validity, given that there was some evidence of statistical heterogeneity (mood and behaviour outcomes).
Schneider (2011)	Not Specified	*Population* – patients with	3 studies	This publication is based on the 2009 Cochrane	Although the

		mild Alzheimer's Disease. *Intervention* – memantine *Comparator* – Placebo *Outcomes* – effect upon ADAS-cog, CIBIC-plus, ADCS-ADL Scale, or the NPI.	N=1282 (last observation carried forward (LOCF)) N=1306 (randomised)	review by the same authors (McShane 2009, above) and includes the same three primary studies. However, this publication reports the results of meta-analyses stratified by severity of AD (mild and moderate AD are reported separately). For patients with mild AD (MMSE scores 20-23), there were no significant differences between memantine and placebo for any of the outcomes assessed: ADAS-Cog, WMD –0.17 (95% CI –1.60 to 1.26), 3 RCTS n=425; CIBIC+, WMD –0.09 (95% CI –0.30 to 0.12), 3 RCTs n=427; ADCS-ADL, WMD 0.62 (95% CI –1.46 to 2.71)), 3 RCTs n=427; neuropsychiatry inventory, WMD 0.09 (95% CI –2.11 to 2.29), 3 RCTs n=427. For patients with moderate AD (MMSE scores 10-19), the results of the meat-analysis for cognitive function favoured memantine; ADCS-Cog WMD –1.33 (95% CI –2.28 to –0.38), RCTs n=682. Meta-analysis for clinical global impression produced borderline results favouring memantine; CIBIC+ WMD –0.16 (–0.32 to –0.00), 3 RCTs n=392. There were no significant differences between memantine and placebo for ADCS-ADL or the neuropsychiatry inventory.	review methods specify the involvement of two reviewers in study selection (minimising the potential for error and/or bias), it is not clear whether two reviewers were involved throughout the review process (data extraction and quality assessment). Pooled estimates of clinical effectiveness (particularly the use of a fixed effects model) are of questionable validity, given

					that there was some evidence of statistical heterogeneity (mood and behaviour outcomes).

RCTs/DTAs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Pomera (2007)	*Population* - All participants met clinical diagnostic criteria for probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association. 6 Patients had a Mini-Mental State Examination score between 10 and 22 at both screening and baseline7; were 50 years of age or older; had brain imaging within the previous 12 months consistent with a diagnosis of AD; had a knowledgeable caregiver; resided in the community; were ambulatory; and were medically stable. Patients were permitted to receive stable treatment with antihypertensives, anti-inflammatories, diuretics, laxatives, antidepressants, and tocopherol. *Intervention* - participants were assigned to memantine (10 mg	N=403 (recruited) N=394 (included in the analyses)	This article reports the data on the significant outcome measure (ADAS-Cog) from one of the trials included in the Cochrane review (McShane et al 2009) detailed above. Participants in the memantine group showed significantly less decline in cognitive function (measured by change in ADAS-Cog from baseline) at 8, 12, 18, and 24 weeks (p-values only reported). When data were stratified by sub-scale, results favoured the memantine group for the language subscale (mean (SE) change from baseline: placebo 0.792 (0.203), memantine 0.169 (0.203), p=0.002) and for the memory sub-scale (mean (SE) change from baseline: placebo 0.481 (0.381), memantine -0.506 (0.381), p=0.018). There was no significant difference between the memantine and placebo groups for the praxis sub-scale of ADAS-Cog.	Based on information reported in the Cochrane systematic review (McShane et al 2009, see above), this publication selectively reports only the significant outcome measure from an RCT which assessed a number of additional outcomes. Data were for a

	twice daily) Memantine was initiated at 5 mg/d and titrated with 5mg weekly increments. *Comparator* – Placebo *Outcome* – ADAS-cog score			modified ITT analysis, where participants included in the analysis received at least 1 dose of study medication and 1 post-baseline assessment (9 of the original 403 participants were therefore excluded).
Modrego (2010)	*Population* - patients fulfilling the NINCDS-ADRDA work group criteria for probable AD. The patients included scored more than 15 points in the mini-mental test (Spanish version with a maximum possible score of 35 points) and be in the stages 1 or 2 of the Clinical Dementia Rating Scale (CDR). *Intervention* – memantine hydrochloride 20 mg/daily. *Comparator* - donepezil hydrochloride 5 mg/daily to reach the dose of 10 mg/daily after 1 month *Outcome(s) – (i).* whether memantine induces changes in brain metabolite concentrations in comparison with donepezil in the early stages of AD; *(ii)*	N= 67 (randomised) N= 63 (completed the trial and included in analyses)	This article reports data on mean (SD) change from baseline to six months in the Alzheimer's Disease Assessment Scale (ADAS-Cog), neuropsychiatric inventory (NPI) and disability assessment for Dementia (DAD). For both the memantine and the donepezil groups, there was deterioration from baseline in all measures. However, this deterioration only reached statistical significance for DAD in the donepezil group where the mean (SD) baseline score was 73.39 (12.69) and the mean (SD) post-treatment score was 66.71 (17.6), p=0.014. There were no significant differences in the change from baseline, for any outcome measure, between donepezil and memantine.	The article reported that outcome assessors were blinded, but it was not clear whether other study personnel or participants were also blinded. Patients who did not complete the study were excluded form the analyses. However, excluded

	to observe whether memantine is or is not clinically superior to donepezil in these stages; *(iii)* to explore the capabilities of MRS to monitor progression of AD. *Duration* – 24 Weeks			participants represented <10% of the total study population, and was therefore less likely to have affected results.

Risk of Bias: SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
McShane (2009)	☹	☺	?	☺	?
Schneider (2011)	☺	☺	?	☺	?

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Pomera (2007)	☺	?	☺	☺	☺	☹
Modrego (2010)	☺	☺	?	☺	☺	☺

☺ Low Risk ☹ High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NHS Evidence	memantine	3 relevant guidelines	
DARE	**(memantine) AND (alzheimer* or dementia)**	16 – 9 possibly relevant	3
Primary studies			
CENTRAL	See below	70	3 RCTs, 7 conference abstracts.
MEDLINE		145	
EMBASE		398	
PsychINFO??		130	
Summary		**NA**	

Database: Medline 1950 to present
Search Strategy:
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1 Memantine/ (1308)
2 memantin$.tw. (1543)
3 axura.tw. (5)
4 namenda.tw. (21)
5 ebixa.tw. (14)
6 d145.tw. (17)
7 d-145.tw. (81)
8 Akatinol.tw. (17)
9 ebix.tw. (0)
10 or/1-9 (1846)

11 Alzheimer Disease/ (58769)
12 alzheimer$.ti. (37838)
13 alzheimer$.ab. /freq=2 (16249)
14 Dementia/ (33245)
15 dementia.ti. (24897)
16 dementia.ab. /freq=2 (20878)
17 or/11-16 (94259)
18 10 and 17 (756)
19 randomized controlled trial.pt. (322599)
20 controlled clinical trial.pt. (84057)
21 randomized.ab. (227373)
22 placebo.ab. (130354)
23 Clinical Trials as Topic/ (159645)
24 randomly.ab. (163568)
25 trial.ti. (97823)
26 or/19-25 (749301)
27 exp animal/ not humans/ (3722514)
28 26 not 27 (691355)
29 18 and 28 (243)
30 limit 29 to yr="2006 -Current" (145)

Database: Embase <1980 to 2011 Week 47>
Search Strategy:
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1 Memantine/ (5095)
2 memantin$.tw. (2209)
3 axura.tw. (104)
4 namenda.tw. (244)
5 ebixa.tw. (215)
6 d145.tw. (17)
7 d-145.tw. (95)
8 Akatinol.tw. (115)
9 ebix.tw. (2)

10 or/1-9 (5312)
11 Alzheimer Disease/ (97315)
12 alzheimer$.ti. (47255)
13 alzheimer$.ab. /freq=2 (19777)
14 Dementia/ (59638)
15 dementia.ti. (31607)
16 dementia.ab. /freq=2 (26594)
17 presenile dementia/ (474)
18 or/11-17 (146750)
19 10 and 18 (2954)
20 random$.tw. (666823)
21 factorial$.tw. (17472)
22 (crossover$ or cross-over$).tw. (57147)
23 placebo$.tw. (161729)
24 (doubl$ adj blind$).tw. (119346)
25 (singl$ adj blind$).tw. (11258)
26 assign$.tw. (187017)
27 allocat$.tw. (62833)
28 volunteer$.tw. (146346)
29 Crossover Procedure/ (31241)
30 Double-blind Procedure/ (101771)
31 Randomized Controlled Trial/ (293007)
32 Single-blind Procedure/ (14465)
33 or/20-32 (1108482)
34 (animal/ or nonhuman/) not human/ (4306060)
35 33 not 34 (969973)
36 19 and 35 (509)
37 limit 36 to yr="2006 -Current" (398)

Database: PsycINFO <1987 to November Week 4 2011>
Search Strategy:
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1 memantin$.tw. (690)

2 axura.tw. (0)
3 namenda.tw. (4)
4 ebixa.tw. (1)
5 d145.tw. (0)
6 d-145.tw. (1)
7 Akatinol.tw. (2)
8 ebix.tw. (0)
9 Alzheimer Disease/ (24659)
10 alzheimer$.ti. (16922)
11 alzheimer$.ab. /freq=2 (6582)
12 Dementia/ (19610)
13 dementia.ti. (15091)
14 dementia.ab. /freq=2 (15322)
15 presenile dementia/ (132)
16 or/1-8 (691)
17 or/9-15 (41604)
18 16 and 17 (367)
19 clinical trials/ (5518)
20 random$.ti,ab. (86493)
21 groups.ti,ab. (225375)
22 (double adj3 blind).ti,ab. (12597)
23 (single adj3 blind).ti,ab. (1041)
24 experimental design/ (5396)
25 controlled.ti,ab. (53584)
26 (clinical adj3 study).ti,ab. (4965)
27 trial.ti,ab. (43774)
28 treatment outcome clinical trial.md. (20138)
29 or/19-28 (357634)
30 18 and 29 (156)
31 limit 30 to yr="2006 -Current" (130)

CENTRAL on The Cochrane Library
ID Search

#1	MeSH descriptor Memantine, this term only
#2	memantin*
#3	axura
#4	namenda
#5	ebixa
#6	d124
#7	"d-145"
#8	akatinol
#9	ebix
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11	MeSH descriptor Alzheimer Disease, this term only
#12	MeSH descriptor Dementia, this term only
#13	dementia:ti
#14	alzheimer*
#15	(#11 OR #12 OR #13 OR #14)
#16	(#10 AND #15)
#17	(#16), from 2006 to 2011