BEST in Mental Health
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Best Evidence Summaries of Topics in Mental Healthcare

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

Question

For people with Alzheimer's disease, vascular dementia or Lewy Body dementia, how effective is Memantine compared with other medication, treatment as usual or no treatment, in reducing problematic behaviour?

Clarification of question using *PICO* structure

Patients:	People with Alzheimer's disease, vascular dementia or Lewy Body dementia
Intervention:	Memantine
Comparator:	Other medication, treatment as usual or no treatment
Outcome:	Problematic behaviour

Plain language summary

There is no high quality research evidence to suggest that Memantine is any more effective than any other treatment or intervention in reducing problematic behaviour in people with Alzheimer's disease or Dementia

Clinical and research implications

Evidence from one moderate quality randomised trial showed that memantine with donepezil significantly improved behaviour after 24 weeks of treatment. However, three trials found no evidence that memantine monotherapy was more effective than placebo in behavioural or cognitive outcomes. This finding is consistent with the NICE guideline recommendation which did not find a statistically significant benefit for memantine on behavioural outcomes measured by the NPI and BGP. It is also consistent with the Scottish Medicines Consortium guidance which stated that there was insufficient evidence to recommend the use of memantine in people with dementia.

More randomised, placebo-controlled trials of patients with Alzheimer's disease in outpatient settings which measure behaviour are needed.

What does the evidence say?

Number of included studies/reviews (number of participants)

One systematic review (3 trials, 1006 patients) and one randomised trial (369 patients) were included. All the studies were in patients with moderate to severe Alzheimer's disease.

Main findings

There was no significant difference between memantine and placebo after 24 weeks of therapy in measures of behaviour (Neuropsychiatric Inventory (NPI)) or cognition (Severe Impairment Battery (SIB)) in the randomised trial.

The review contained one trial of combination memantine therapy (with donepezil) and two trials of memantine monotherapy for between 24 and 28 weeks, all compared with placebo. Memantine combination therapy had significantly greater improvements in behaviour (NPI and the Behavioural Rating Scale for Geriatric Patients (BGP)) compared with placebo. The two trials of memantine alone did not find any statistically significant differences between memantine and placebo in NPI and BGP scores. However there were some significant improvements in some of the NPI subdomains (delusions, agitation/aggression, irritability/lability; and appetite/eating) with memantine monotherapy in two of the trials.

Authors' conclusions

The trial concluded that it failed to show the superiority of memantine in a group of patients with moderate to severe Alzheimer's disease and significant baseline agitation and aggression, but that methodological limitations may have contributed to the negative result. The review concluded that the current data provides evidence that memantine may be effective in alleviating or preventing

behavioural symptoms in patients with moderate to severe Alzheimer's disease living in the community.

Reliability of conclusions/Strength of evidence

The trial and the review were both of moderate quality and had some limitations. The trial was fully blinded, using an identical placebo treatment, but it was unclear if the randomisation was concealed until the point of patient assignment and 17% of the patients were excluded from the analysis. The main limitation of the review was the literature search, which covered only two databases and was restricted to studies published in English. It also did not provide any details of the patients or designs of the three trials, which makes it difficult to judge the generalisability of the results.

Overall, there was a small amount of moderate quality evidence available for the effectiveness of memantine in patients with moderate to severe Alzheimer's disease.

What do guidelines say?

The National Institute for Health and Clinical Excellence guidelines, 'Donepezil, Galantamine, Rivastigmine and Memantine for the treatment of Alzheimer's Disease' (2011), make the following comments on the use of Memenatine for problematic behaviour:

"4.1.35. The study for memantine monotherapy that was published after 2004 and included by the Assessment Group measured behavioural outcomes using NPI and the Behavioural Rating Scale for Geriatric Patients (BGP). Neither measure showed a statistically significant benefit of memantine. The data were pooled with the existing data at 24–28 weeks, which did not show a statistically significant gain from memantine compared with placebo (a mean change from baseline versus placebo of -1.608 (p = 0.314) at 24–28 weeks using NPI score). The results of the meta-analysis by the manufacturer of memantine in moderate to severe disease showed a statistically significant (p = 0.03) benefit in terms of NPI and NPI-Nursing Home version (standardised mean difference = -0.12, p = 0.03)."

The Scottish Intercollegiate Guidance Network guidelines, 'Management of people with Dementia' (2006) make the following comments on the use of Memenatine for problematic behaviour:

"The efficacy of memantine has been examined in people with moderate to severe Alzheimer's disease and mild to moderate vascular dementia.123-127
After six months of treatment with 20 mg of memantine per day, there was a small, although not clinically significant, benefit over a wide range of outcome measures in patients with mild to moderate vascular dementia… The Scottish Medicines Consortium (SMC) assessment of memantine concluded that the magnitude of any beneficial effect was small and the clinical importance unclear (www.scottishmedicines.org.uk). There is currently insufficient evidence to recommend the use of memantine for the treatment of core or associated symptoms in people with dementia"

Date question received: 22/09/15
Date searches conducted: 23/09/15
Date answer completed:

References

Systematic reviews

1. Grossberg, G. T., Pejović, V., Miller, M. L., & Graham, S. M. (2009). Memantine therapy of behavioral symptoms in community-dwelling patients with moderate to severe Alzheimer's disease. *Dementia and geriatric cognitive disorders*, 27(2), 164-172.

Randomised controlled trials

2. Herrmann, N., Gauthier, S., Boneva, N., & Lemming, O. M. (2013). A randomized, double-blind, placebo-controlled trial of memantine in a behaviorally enriched sample of patients with moderate-to-severe Alzheimer's disease. *International Psychogeriatrics*, 25(6), 919.

Guidelines

The National Institute for Health and Care Excellence (2011) *Donepezil, Galantamine, Rivastigmine and Memantine for the treatment of Alzheimer's Disease.* Information about NICE technology appraisal guidance 217 http://www.nice.org.uk/guidance/ta217

The Scottish Intercollegiate Guidance Network. (2006) Management of patients with dementia. SIGN 86. 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
Grossberg et al (2009)	01/1992 to 10/2008	***Participants*:** Community-dwelling patients with moderate to severe Alzheimer's disease. ***Intervention*:** Memantine prescribed at 20 mg/day over 24/28 weeks. Monotherapy (Memantine only) was given in two studies, and combined therapy (Memantine and Donepezil) was given in one study ***Comparator*:** Placebo (two studies) or placebo with donepezil (one study) ***Outcome*:** Behavioural outcomes measured by the Neuropsychiatric Inventory (NPI; used in all three studies) and Behavioural Rating Scale for Geriatric Patients (BGP; used in	3 (n =1006)	All 3 trials satisfied most of the items in the CONSORT scale, scoring yes for between 18 and 22 out of the 22 items. The study of memantine and donepezil combination therapy showed a significantly greater improvement in NPI (Cohen's d effect size (ES) -0.30, -0.51 to -0.10) and BGP scores (ES -0.34, -0.55 to -0.13) with memantine therapy. There was no statistically significant difference between memantine monotherapy and placebo in the change in NPI score (study 1 ES: -0.21, 95% CI -0.45 to 0.04; study 2 ES: -0.05, 95% CI -0.27 to 0.17). Nor was there any difference in the change in BGP score in one monotherapy study (ES: -0.14, 95% CI -0.37 to 0.09). There were also significantly greater	Moderate The inclusion and exclusion criteria were specified for the review. The literature search only included 2 databases, with no attempts to locate other material and was restricted to English language so some studies may have been missed. No details were provided of the review methods.

		two studies) ***Study design*:** Randomised, double blind, placebo-controlled trials		improvements in the NPI domains of delusions, agitation/aggression, irritability/lability and appetite/eating change for memantine compared with placebo (two studies).	The quality of the studies was assessed using the CONSORT statement, but the synthesis was poor as no details of the patients were provided.

Randomised controlled trials

Author (year)	**Inclusion criteria**	**Number of participants**	**Summary of results**	**Risk of bias**
Herrmann et al (2013)	***Participants*:** Patients aged at least 50 years with a moderate to severe Alzheimer's Disease (NPI total score ≥ 13 and agitation/aggression score ≥ 1), Mini-Mental State Examination score ≥ 8 and ≤ 18; ongoing therapy with donepezil, galantamine or rivastigmine for the last 6 months and on a stable dose for the 3 months prior to screening. ***Intervention*:** Memantine starting at 5 mg/day titrated up to 20mg/day by week 4, given for 24 weeks. ***Comparator*:**	N=369 (n=182 memantine, n=187 placebo)	The mean patient age was 75 years, 42% were male, 84% had Alzheimer's disease for more than 3 years, and the mean baseline outcome measures were: MMSE score 11.9, NPI score 30 and SIB score 82. After 24 weeks 17% of the patients in each group had discontinued the intervention and were excluded from the analysis. The analysis of the change from baseline to week 24 showed no statistically significant differences between memantine and placebo for behaviour (NPI score mean difference 1.23, 95% CI -1.75 to 4.21) or cognition (SIB score mean difference -0.48, 95% CI -2.30 to 1.34).	Moderate The randomisation list was produced following a standard procedure but it was unclear if there was any allocation concealment. All patients, care givers and raters were blind to

	Placebo given for 24 weeks. ***Outcomes*:** Primary: behaviour measured by the Neuropsychiatric Inventory (NPI) and cognition measured by the Severe Impairment Battery (SIB). Secondary: Caregiver assessment measures of change and activities of daily living, patient's agitated behaviour (Cohen-Mansfield Agitation Inventory (CMAI)).		Both groups showed improvements in NPI during the study but a decline in the SIB score. There were also no statistically significant between group differences for any of the secondary outcomes.	treatment. Not all randomised patients were included in the analysis (17% were excluded in each group). All outcomes were reported.

Risk of bias

Systematic reviews

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review process	Quality assessment	Synthesis
Grossberg (2009)	☺	☹	?	☺	☹

Randomised controlled trials

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Herrmann (2013)	☺	?	☺	☺	☹	☺

☺ Low risk ☹ High risk ? Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
Guidelines			
NICE and SIGN	Memantine, Behaviour	7	2
Systematic Reviews			
MEDLINE	1 exp Alzheimer Disease/ 74023 2 exp Dementia, Vascular/ 5712 3 exp Lewy Body Disease/ 2333 4 Lewy Body Dementia.ab,ti. 509 5 "alzheimer*".ab,ti. 103331 6 1 or 2 or 3 or 4 or 5 118071 7 exp Memantine/ 1780 8 memantine.ab,ti. 2475 9 7 or 8 2751 10 exp Drug Therapy/ 1119925 11 "medication*".ab,ti. 220860 12 ((pharmacological or medic*) adj (treatment* or therap*)).ab,ti. 83261 13 treatment as usual.ab,ti. 2113 14 TAU.ab,ti. 28084 15 10 or 11 or 12 or 13 or 14 1391442 16 ((problem* or challeng* or disrupt* or negative) adj behavio*).ab,ti. 8700 17 6 and 9 and 15 442 18 – 36 Medline Systematic Review filter applied 37 17 and 36 71	71	0
EMBASE	1 exp Alzheimer Disease/ 138615 2 exp Dementia, Vascular/ 9303 3 exp Lewy Body Disease/ 4747 4 Lewy Body Dementia.ab,ti. 846	144	0

	5 "alzheimer*".ab,ti. 132634 6 1 or 2 or 3 or 4 or 5 167714 7 exp Memantine/ 7775 8 memantine.ab,ti. 3636 9 7 or 8 8001 10 exp Drug Therapy/ 1998788 11 "medication*".ab,ti. 330192 12 ((pharmacological or medic*) adj (treatment* or therap*)).ab,ti. 119574 13 treatment as usual.ab,ti. 2794 14 TAU.ab,ti. 26649 15 10 or 11 or 12 or 13 or 14 2288599 16 ((problem* or challeng* or disrupt* or negative) adj behavio*).ab,ti. 10597 17 6 and 9 and 15 1848 18 - 47 EMBASE Systematic Review filters applied 48 17 and 47 244 49 48 244 50 limit 49 to yr="2010 - 2015" 144		
PsycINFO/CINAHL	1 exp Alzheimer Disease/ 34508 2 exp Lewy Body Disease/ 1325 3 Lewy Body Dementia.ab,ti. 294 4 "alzheimer*".ab,ti. 43198 5 memantine.ab,ti. 1070 6 exp Drug Therapy/ 105939 7 "medication*".ab,ti. 62927 8 ((pharmacological or medic*) adj (treatment* or therap*)).ab,ti. 13243 9 treatment as usual.ab,ti. 1856 10 TAU.ab,ti. 5526 11 ((problem* or challeng* or disrupt* or negative) adj behavio*).ab,ti. 17093 12 6 or 7 or 8 or 9 or 10 153182 13 exp Vascular Dementia/ 1859 14 1 or 2 or 3 or 4 or 13 45423	80	3

	15 5 and 12 and 14 405 16 - 25 PsycINFO systematic Review filter applied 26 15 and 25 80 80		
Primary Studies			
MEDLINE	1 exp Alzheimer Disease/ 74023 2 exp Dementia, Vascular/ 5712 3 exp Lewy Body Disease/ 2333 4 Lewy Body Dementia.ab,ti. 509 5 "alzheimer*".ab,ti. 103331 6 1 or 2 or 3 or 4 or 5 118071 7 exp Memantine/ 1780 8 memantine.ab,ti. 2475 9 7 or 8 2751 10 exp Drug Therapy/ 1119925 11 "medication*".ab,ti. 220860 12 ((pharmacological or medic*) adj (treatment* or therap*)).ab,ti. 83261 13 treatment as usual.ab,ti. 2113 14 TAU.ab,ti. 28084 15 10 or 11 or 12 or 13 or 14 1391442 16 ((problem* or challeng* or disrupt* or negative) adj behavio*).ab,ti. 8700 17 6 and 9 and 15 442 18 - 25 RCT Filters applied 26 17 and 25 62	62	0
EMBASE	1 exp Alzheimer Disease/ 138615 2 exp Dementia, Vascular/ 9303 3 exp Lewy Body Disease/ 4747 4 Lewy Body Dementia.ab,ti. 846 5 "alzheimer*".ab,ti. 132634 6 1 or 2 or 3 or 4 or 5 167714 7 exp Memantine/ 7775 8 memantine.ab,ti. 3636	167	1

	9 7 or 8 8001 10 exp Drug Therapy/ 1998788 11 "medication*".ab,ti. 330192 12 ((pharmacological or medic*) adj (treatment* or therap*)).ab,ti. 119574 13 treatment as usual.ab,ti. 2794 14 TAU.ab,ti. 26649 15 ((problem* or challeng* or disrupt* or negative) adj behavio*).ab,ti. 10597 16 10 or 11 or 12 or 13 or 14 2288599 17 6 and 9 and 16 1848 18 - 24 RCT Filters applied 25 17 and 24 267 26 25 267 27 limit 26 to yr="2010 - 2015" 167		
PsycINFO/CINAHL	1 exp Alzheimer Disease/ 34508 2 exp Lewy Body Disease/ 1325 3 Lewy Body Dementia.ab,ti. 294 4 "alzheimer*".ab,ti. 43198 5 memantine.ab,ti. 1070 6 exp Drug Therapy/ 105939 7 "medication*".ab,ti. 62927 8 ((pharmacological or medic*) adj (treatment* or therap*)).ab,ti. 13243 9 treatment as usual.ab,ti. 1856 10 TAU.ab,ti. 5526 11 ((problem* or challeng* or disrupt* or negative) adj behavio*).ab,ti. 17093 12 6 or 7 or 8 or 9 or 10 153182 13 exp Vascular Dementia/ 1859 14 1 or 2 or 3 or 4 or 13 45423 15 5 and 12 and 14 405 16 - 21 RCT filters applied 22 15 and 21 148 23 22 148	70	2

	24 limit 23 to yr="2010 - 2015" 70		

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