Best Evidence Summaries of Topics in Mental Healthcare

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

Question

For people with Alzheimer's or mixed dementia how effective are cholinesterase inhibitors augmented with memantine compared to cholinesterase inhibitors (ChEI) alone / placebo in achieving improved outcomes in terms of cognition, function, delay to institution, and carer burden / stress?

Clarification of question using PICO structure

Patients: People with Alzheimer's dementia (AD) or mixed dementia
Intervention: Cholinesterase inhibitors (ChEI) augmented with memantine
Comparator: Cholinesterase inhibitors (ChEI) alone or placebo
Outcome: Improved outcomes (cognition, function, delay to institution, carer burden)

Clinical and research implications

Two systematic reviews, of moderate to high quality, provided evidence to inform this summary. The reviews were only able to identify a small number of RCTs (a total of four different studies, with two RCTs being common to both reviews). Both reviews reported some evidence of a small benefit from adding memantine to donepezil in patients with moderate to severe Alzheimer's disease; outcomes assessed included clinical global score, cognition, function, and behaviour and mood. When patients with mild Alzheimer's disease were included in the analyses (one review), only function was significantly improved by the addition of memantine. The authors of both reviews concluded that it is currently unclear clinically significant outcomes can be achieved using combination therapy. These conclusions are a reasonable interpretation of the available evidence and are likely to be reliable.

Further studies are needed to confirm the findings of the two systematic reviews included in this assessment. More data are particularly needed for patients with mild Alzheimer's disease and for patients with other dementias; no studies which included participants with any other dementia types were identified. Studies assessing combination therapy using memantine and ChEIs other than donepezil may also be useful.

What does the evidence say?

Number of included studies/reviews (number of participants)
We identified two systematic reviews which were relevant to this evidence summary.[1,2] Both reviews aimed to compare the effectiveness of combination therapy with memantine and

cholinesterase inhibitors (ChEI) with monotherapy. In one review, the monotherapy comprised ChEI,[1] and in the other the monotherapy could be either ChEI or memantine.[2] Each review included three blinded randomised controlled trials (RCTs) and two RCTs were common to both reviews. The second review also included ten studies of other designs, but minimal results were reported for these studies.[2] All studies included in both reviews were conducted solely in patients with Alzheimer's disease (AD) and the ChEI used in all studies was donepezil;[1,2] no studies which included participants with any other dementia types were identified. One review focussed on patients with moderate to severe AD,[1] and the other included patients with all stages of AD as well as subgroup analyses of patients with moderate to severe AD.[2]

Main Findings

Both systematic reviews found small but statistically significant benefits associated with the use of mamantine in combination with donepezil, compared to donepezil alone, in patients with moderate to severe AD.[1,2] One review showed improvements in clinical global score (SMD -0.20 (95% CI: -0.32 to -0.09)), cognition (SMD -0.25 (95% CI: -0.36 to -0.14)) and behaviour and mood (SMD -0.17 (95% CI: -0.32 to -0.03)), but no significant effect on function.[1] The second review showed improvements in cognition (SMD 0.45 (95% CI: 0.27 to 0.63)), function (SMD 0.23 (95% CI: 0.06 to 0.40)) and behaviour and mood (SMD 4.4 (95% CI: 3.01 to 5.70)).[2] Analyses from the second review, which included patients with mild AD, indicated that the addition of memantine to donepezil was associated with improvements in function only (SMD 1.07 (95% CI: 0.02 to 1.89)).[2]

Authors Conclusions

The authors of both reviews concluded that, though there was some evidence of a small benefit from adding memantine to donepezil in patients with moderate to severe AD, it is currently unclear clinically significant outcomes can be achieved using combination therapy and more research is therefore needed.

Reliability of conclusions/Strength of evidence

Two systematic reviews, of moderate to high quality, provided evidence to inform this summary. The reviews were only able to identify a small number of RCTs (a total of four different studies, with two RCTs being common to both reviews). Whilst both reviews reported some evidence of a small benefit from adding memantine to donepezil in patients with moderate to severe Alzheimer's disease, the authors concluded that it is currently unclear clinically significant outcomes can be achieved using combination therapy. These conclusions are a reasonable interpretation of the available evidence and are likely to be reliable.

What do guidelines say?

UK clinical guidelines do not make any recommendations for augmenting ChEIs with memantine. NICE clinical guideline CG42 recommends memantine as a treatment option for people with a moderate stage of Alzheimer's disease who are intolerant or have a contraindication to ChEIs. Memantine is also recommended as a treatment option for those with severe Alzheimer's disease.

The systematic reviews included in this evidence summary do not provide any strong evidence to support the use of combination therapy and are therefore in line with current guidance.

Date question received: 14/05/2013
Date searches conducted: 16/05/2013
Date answer completed: 24/05/2013

References

Systematic Reviews

1. Farrimond L, Roberts E, McShane R. Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review. BMJ Open 2012;2:e000917

RCT's

2. Muayqil T, Camicioli R. Systematic Review and Meta-Analysis of combination Therapy with cholinesterase Inhibitors and Memantine in Alzheimer's Disease and Other dementias. Dementia and Geriatric Cognitive Disorders Extra 2012 2:546–572

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Farrimond (2012)	3/5/2011	*Participants* – Study participants were required to have a diagnosis of moderate to severe Alzheimer's disease (AD) and to be taking AChEIs. *Intervention* – Addition of memantine to AChEI *Comparison* – Placebo *Outcomes* – Primary outcomes were clinical global impression, cognitive function, functional performance in ADL and behavioural and mood disturbance. *Study design* – Randomised, double blind parallel group, placebo-controlled trials were eligible for inclusion in this review. Included studies were also required to specify their sample selection criteria, use	3 studies were included (N=1317)	This review aimed to compare the efficacy of acetylcholinesterase inhibitors (AChEI) in combination with memantine to AChEI alone, in patients with moderate-to-severe Alzheimer's disease (AD). Three RCTs (two of which were included in TA217, which informed current NICE guidance) were included in this review. All study participants were diagnosed based on their Mini Mental State Examination (MMSE) score. Two studies included only participants with moderate to severe AD and the remaining study was conducted in participants with mild to moderate AD, with subgroup data available for moderate disease (only the subgroup data were used in the meta-analyses). Where reported the mean age of study participants was approximately 75 years. The two trials previously included in TA217 compared the addition of either 20mg per day memantine or placebo in patients already receiving stable treatment with donepezil. The third, un-published trial compared the addition of memantine extended release 28mg daily to placebo in patients receiving a stable dose of any AChEI; this trail was not eligible for inclusion in the NICE assessment, because this formulation of memantine is not currently licensed in Europe.	A clear research question was reported and appropriate inclusion criteria were defined. The Cochrane Dementia and Cognitive Improvement Group's trail register (which searches 6 bibliographic databases + CENTRAL and trials other registers) was searched for relevant studies. Additional searches included international and company databases

		established diagnostic criteria and specify outcome measures.		Outcomes were assessed at six months, using Clinician's Interview-Based Impression of Change plus caregiver's input (CIBIC-plus) scale, the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) and Severe Impairment Battery (SIB), the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) scale and the Neuropsychiatric Inventory (NPI). Data were pooled using a random effects model and standardised mean difference (SMD), to allow pooling of data from studies which used different measurement scales to assess the same outcome. The risk of bias of included studies was judged to be low. The results of meta-analyses indicated that the addition of memantine to AChEI therapy had a small, but statistically significant, beneficial effect on clinical global score (SMD -0.20 (95% CI: -0.32 to -0.09)), cognition (SMD -0.25 (95% CI: -0.36 to -0.14)) and behaviour and mood (SMD -0.17 (95% CI: -0.32 to -0.03)), but no significant effect on function, in patients with moderate to severe AD.	and conference abstracts. Data were independently extracted by two reviewers, but it was unclear whether similar measures to reduce error/bias were applied to the study selection process. The risk of bias in included studies was assessed using the Cochrane risk of bias tool (full results published in a Cochrane review). The validity of pooling data from studies which used different measurement scales is questionable (not

					undertaken in TA217), however, this issue only applied to measures of cognition.
Muayqil (2012)	March 2012	*Population* – Participants included were community living adults >18 years of age with a diagnosis of a degenerative or vascular dementia, as defined in the primary studies. Studies of patients with dementias due to conditions such as metabolic, traumatic, inflammatory, drug or malignant processes were excluded. *Intervention* – ChEI with memantine (any route of administration, dose, or duration). *Comparison* – Memantine or ChEI alone. *Outcome* - Primary outcomes were changes in cognitive ability and functional ability. Secondary outcome	13 studies were included (3 blinded RCTs n=971)	This review aimed to compare the efficacy and safety of combination therapy with memantine and a cholinesterase inhibitor (ChEI) to monotherapy with either memantine or a ChEI for the treatment of dementia. The review included 3 blinded RCTs (n=971), 2 open label RCTs (n=433), 3 non-randomised comparative studies (n=924), and 5 observational studies with no comparator group (n=472). All comparative studies compared memantine combined with ChEI to ChEI alone, with the exception of one three-arm RCT that compared memantine combined with ChEI to ChEI alone or memantine alone. All studies were conducted in participants with AD. Only the three blinded RCTs were included in the meta-analysis. Two of these trials were the fixed dose memantine studies included in the Farrimond review described above, however, in the Muayqil review, participants with mild AD were not excluded from the analyses. The third study was a three-arm RCT comparing 20 mg per day memantine + 10 mg per day donepezil with 10 mg per day donepezil alone or 20 mg per day memantine alone and was conducted in patients with moderate to severe AD and a mean age of approximately 76 years. The	A clear research question was reported and the inclusion criteria were defined, however, only English language studies were included, raising the possibility of language bias/omission of relevant studies. Three bibliographic databases, trials registries and conference proceedings were searched and searches were supplemented by screening the bibliographies of

		measures were clinical global impression, institutionalisation rates (of community-dwelling patients), behavioural changes, quality of life, and death rates. Adverse events were also reported. *Study design* – English language studies were included in this review, studies could be blinded or open label randomised controlled trials (RCTs), quasi RCTs, non-RCTs, cohort studies, or case-control studies.		proportion of female participants in the three RCTs ranged from 52% to 66%. Cognitive outcomes were assessed using MMSE ADAS-Cog and SIB. Functional outcomes were assessed using ADCS-ADL and the Bristol Activities of Daily Living Scale (BADLS). Behavioural outcomes were assessed using NPI and the Behavioural Rating Scale for Geriatric Patients care dependency subscale. Treeatment durations were not reported. Data were pooled using a random effects model and standardised mean difference (SMD), to allow pooling of data from studies which used different measurement scales to assess the same outcome. This additional blinded RCT was rated as having low risk of bias. The results of meta-analyses indicated that the addition of memantine to ChEI, in patients with mild to severe AD did not significantly improve cognitive or behavioural outcomes, but did improve functional outcomes (SMD 1.07 (95% CI: 0.26 to 1.89)), based on data from all three studies. Subgroup analysis, including only participants with moderate to severe AD (2 studies, n=626), indicated that in this patient groups cognitive (SMD 0.45 (95% CI: 0.27 to 0.63)), functional (SMD 0.23 (95% CI: 0.06 to 0.40)) and behavioural (SMD 4.4 (95% CI: 3.01 to 5.59)) outcomes were improved when patients were treated with combination therapy, compared to ChEI alone. No significant differences in adverse event rates were identified. Seven of the ten remaining studies suggested a benefit for combination therapy; results were reported by treatment group,	reviews and contact with study authors. In order to minimise the potential for error/bias in the review process, study selection and data extraction processes were carried out by two reviewers. The risk of bias in included RCTs was assessed using the Cochrane risk of bias tool and observational studies were assessed using the Newcastle-Ottawa scale. Broadly appropriate meta-analytic methods were used,

				but without estimates of between group differences.	however, the validity of pooling data from studies which used different measurement scales is questionable.

Risk of Bias: SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Farrimond (2012)	☺	☺	?	☺	?
Muayqil (2012)	☹	☺	☺	☺	?

☺ Low Risk ☹ High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Memantine	13	1
DARE	1 (alzheimer*) IN DARE, HTA 369 Delete 2 MeSH DESCRIPTOR Alzheimer Disease EXPLODE ALL TREES 254 Delete 3 (*cholinesterase) IN DARE, HTA 114 Delete 4 (donepezil) IN DARE, HTA 73 Delete 5 (galantamine) IN DARE, HTA 49 Delete 6 (rivastigmine) IN DARE, HTA 55 Delete 7 (Aricept) IN DARE, HTA 7 Delete 8 (E2020) IN DARE, HTA 4 Delete 9 (galanthamin*) IN DARE, HTA 8 Delete 10 (galantamin*) IN DARE, HTA 49 Delete 11 (reminyl) IN DARE, HTA 5 Delete 12 (exelon) IN DARE, HTA 6 Delete 13 (ENA 713) IN DARE, HTA 3 Delete 14 MeSH DESCRIPTOR Cholinesterase Inhibitors EXPLODE ALL TREES 85 Delete 15 MeSH DESCRIPTOR Galantamine EXPLODE ALL TREES 24 Delete 16 MeSH DESCRIPTOR Tacrine EXPLODE ALL TREES 4 Delete 17 (tacrin*) IN DARE, HTA 23 Delete 18 (reminyl) IN DARE, HTA 5 Delete 19 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17		

	OR #18 172 Delete 20 #1 OR #2 419 Delete 21 #19 AND #20 116 Delete 22 (memantin*) IN DARE, HTA 46 Delete 23 MeSH DESCRIPTOR Memantine EXPLODE ALL TREES 41 Delete 24 #22 OR #23 59 Delete 25 #21 AND #24 29 Delete		
Primary studies			
CENTRAL	#1 MeSH descriptor: [Cholinesterase Inhibitors] explode all trees 794 #2 MeSH descriptor: [Memantine] explode all trees 171 #3Enter terms for searc#1 and #229 #4Enter terms for searc2012 17201 #5Enter terms for searc2013 50268 #6Enter terms for searc2014 117 #7Enter terms for searc#4 or #5 or #6 60899 #8Enter terms for searc#3 and #718 Central only 1	1	
PsycINFO	1. PsycINFO; ALZHEIMER'S DISEASE/ OR exp DEMENTIA/; 48010 results. 2. PsycINFO; alzheimer's.ti,ab; 31334 results. 3. PsycINFO; "mixed dementia".ti,ab; 245 results. 4. PsycINFO; 1 OR 2 OR 3; 52651 results.	5	

	5. PsycINFO; exp CHOLINESTERASE INHIBITORS/; 2178 results. 6. PsycINFO; memantine.ti,ab; 822 results. 7. PsycINFO; augment*.ti,ab; 14417 results. 8. PsycINFO; 5 AND 6 AND 7; 4 results. 11. PsycINFO; 5 AND 6; 84 results. 12. PsycINFO; 4 AND 11; 80 results. 13. PsycINFO; 12 [Limit to: Publication Year 2012-Current]; 5 results		
Embase	13. EMBASE; ALZHEIMER'S DISEASE/ OR exp DEMENTIA/; 207985 results. 14. EMBASE; alzheimer's.ti,ab; 90325 results. 15. EMBASE; "mixed dementia".ti,ab; 532 results. 16. EMBASE; 13 OR 14 OR 15; 220694 results. 17. EMBASE; exp CHOLINESTERASE INHIBITORS/; 63699 results. 18. EMBASE; memantine.ti,ab; 2816 results. 19. EMBASE; augment*.ti,ab; 133905 results. 20. EMBASE; 17 AND 18 AND 19; 9 results. 21. EMBASE; 17 AND 18; 1007 results. 22. EMBASE; 16 AND 21; 930 results. 23. EMBASE; 22 [Limit to: Publication Year 2012-Current]; 193	64	

	results. 24. EMBASE; random*.ti,ab; 800571 results. 25. EMBASE; factorial*.ti,ab; 20676 results. 26. EMBASE; (crossover* OR cross-over*).ti,ab; 65360 results. 27. EMBASE; placebo*.ti,ab; 187989 results. 28. EMBASE; (doubl* ADJ blind*).ti,ab; 136050 results. 29. EMBASE; (singl* ADJ blind*).ti,ab; 13265 results. 30. EMBASE; assign*.ti,ab; 220501 results. 31. EMBASE; allocat*.ti,ab; 75019 results. 32. EMBASE; volunteer*.ti,ab; 166928 results. 33. EMBASE; CROSSOVER PROCEDURE/; 36827 results. 34. EMBASE; DOUBLE BLIND PROCEDURE/; 114506 results. 35. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 341966 results. 36. EMBASE; SINGLE BLIND PROCEDURE/; 17352 results. 37. EMBASE; 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36; 1304691 results. 38. EMBASE; 23 AND 37 [Limit to: Publication Year 2012-Current]; 64 results.		
Medline	14. MEDLINE; ALZHEIMER'S DISEASE/ OR exp DEMENTIA/; 112416 results.	38	

	15. MEDLINE; alzheimer's.ti,ab; 70796 results. 16. MEDLINE; "mixed dementia".ti,ab; 364 results. 17. MEDLINE; 14 OR 15 OR 16; 135832 results. 18. MEDLINE; exp CHOLINESTERASE INHIBITORS/; 40576 results. 19. MEDLINE; memantine.ti,ab; 1959 results. 20. MEDLINE; augment*.ti,ab; 117382 results. 21. MEDLINE; 18 AND 19 AND 20; 6 results. 22. MEDLINE; 18 AND 19; 314 results. 23. MEDLINE; 17 AND 22; 287 results. 24. MEDLINE; 23 [Limit to: Publication Year 2012-Current]; 40 results. 25. MEDLINE; "randomized controlled trial".pt; 352162 results. 26. MEDLINE; "controlled clinical trial".pt; 86276 results. 27. MEDLINE; randomized.ab; 269447 results. 28. MEDLINE; placebo.ab; 145145 results. 29. MEDLINE; "drug therapy".fs; 1619327 results. 30. MEDLINE; randomly.ab; 195995 results. 31. MEDLINE; trial.ab; 278724 results. 32. MEDLINE; groups.ab; 1261789 results. 33. MEDLINE; 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR		

	32; 3142047 results. 34. MEDLINE; 24 AND 33 [Limit to: Publication Year 2012-Current]; 38 results.		
Summary	**NA**	**NA**	

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