Best Evidence Summaries of Topics in Mental Healthcare

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

Question

In people with moderate (including mild-moderate and moderate-severe) dementia how effective are cholinesterase inhibitors when compared to memantine in reducing cognitive or functional decline?

Clarification of question using PICO structure (PICTRO for diagnostic questions)

Patients: people with moderate dementia
Intervention: cholinesterase inhibitors
Comparator: memantine
Outcome: reducing cognitive or functional decline

Clinical and research implications
The available evidence suggests that both the acetylcholinesterase inhibitor donepezil and memantine can offer statistically significant cognitive and functional benefits, which are sustained over one year, and that donepezil can offer clinically significant cognitive benefits. However, there was no evidence for a statistically significant difference in treatment effect (on any outcome measure) between the two treatments. All data were derived from patients with Alzheimer's Disease and studies comparing one acetylcholinesterase inhibitor (donepezil) with memantine; findings may not be generalisable to patients with other types of dementia or to treatment with other acetylcholinesterase inhibitors. Further, adequately powered, RCTs are needed to adequately assess the comparative effectiveness of acetylcholinesterase inhibitors and memantine in reducing cognitive and functional decline in patients with dementia.

What does the evidence say?

Number of included studies/reviews (number of participants)
We identified two RCTs comparing the acetylcholinesterase inhibitor donepezil with memantine in patients with moderate to severe[1] and mild to moderate[2] Alzheimer's Disease (AD); the second study explicitly excluded patients with other types of dementia.

The first study included 295 participants who had been treated with donepezil for a minimum of three months before the study. Participants were randomised to one of four treatment groups: discontinuation of donepezil and placebo memantine; discontinuation of donepezil and active memantine; continuation of donepezil and placebo memantine; continuation of donepezil and active memantine. Outcomes were reported for continuation versus discontinuation of donepezil, active

versus placebo memantine, and for addition of active memantine to donepezil versus addition of placebo memantine to donepezil. No data were reported for the comparison continuation of donepezil plus placebo memantine versus discontinuation of donepezil plus active memantine (i.e. donepezil versus memantine).

The second RCT[2] included 67 participants (of whom 63 completed the study and were included in the analyses) and directly compared donepezil with memantine.

Main Findings

The four arm trial in patients with moderate to severe AD found that patients continuing donepezil had significantly higher average Standardized Mini–Mental State Examination (SMMSE) scores, over the duration of the study, than those discontinuing donepezil (+1.9 points (95% CI: +1.3 to +2.5, P<0.001)), indicating better cognitive function. Patients continuing donepezil also had significantly lower Bristol Activities of Daily Living Scale (BADLS) scores (-3.0 points (95% CI: -1.8 to -4.3, P<0.001)), indicating less functional impairment. Patients receiving active memantine had significantly higher SMMSE scores scores (+1.2 points (95% CI: +0.6 to +1.8, P<0.001)) and lower BADLS scores (-1.5 points (95% CI: -0.3 to -2.8, P = 0.02)) than those receiving placebo.[1] Only the difference in SMMSE score, for patients continuing versus discontinuing donepezil, exceeded the pre-defined minimum clinically important difference (1.4 points for SMMSE and 3.5 points for BADLS). Baseline severity of dementia at significantly influenced the effect of donepezil on SMMSE; a clinically important difference was observed only in patients with moderate dementia. There was no significant benefit of adding memantine to donepezil with respect to SMMSE or BADLS. [1]

The trial which compared donepezil with memantine in patients with mild to moderate AD found no significant differences in decline from baseline, between treatment groups, for any of the outcomes measured (ADAS-Cog, neuropsychiatric inventory (NPI) and disability assessment for dementia (DAD)).[2]

Authors Conclusions

The authors of the four arm trial concluded that, in patients with moderate or severe Alzheimer's Disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months.

The authors of the RCT comparing donepezil with memantine concluded that the two treatments have similar modest clinical effects in patients with mild to moderate AD.

Reliability of conclusions/Strength of evidence

The studies were generally well conducted and reported and the data presented support the authors' conclusions. It should be noted, however, that neither study provides evidence for a significant difference in treatment effect between acetylcholinesterase inhibitors and memantine. Both studies were relatively small and only one was designed to compare one acetylcholinesterase inhibitor (donepezil) with memantine; no studies comparing any other acetylcholinesterase inhibitor with memantine were identified. Both studies were conducted in patients with Alzheimer's Disease and their findings may not be generalisable to patients with other types of dementia. Further, adequately powered, RCTs are therefore needed to determine the comparative effectiveness of acetylcholinesterase inhibitors and memantine in reducing cognitive and functional decline in patients with dementia.

What do guidelines say?

The SIGN guideline on the management of patients with dementia[3] 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.

The NICE guideline on Dementia (CG42)[4] recommends the three acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine as options in the management of cognitive symptoms in people with AD of moderate severity only (MMSE score 10 to 20). The guideline recommends memantine as an option for managing people with moderate AD who are intolerant of or have a contraindication to acetylcholinesterase (AChE) inhibitors or people with severe AD. Memantine is not recommended as a treatment option for people with moderately severe to severe Alzheimer's disease except as part of well-designed clinical studies.
For people with vascular dementia, GC 42 states that acetylcholinesterase inhibitors and memantine should not be prescribed for the treatment of cognitive decline, except as part of properly constructed clinical studies. Similarly, the guideline states that, for people with mild cognitive impairment (MCI), acetylcholinesterase inhibitors should not be prescribed, except as part of properly constructed clinical studies.

NICE guidance on donepezil, galantamine, rivastigmine and memantine for the treatment of AD (NTAG 217, review of NTAG111)[5] recommends the three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as options for managing mild to moderate Alzheimer's disease. The guidance also recommends memantine as an option for managing people with moderate AD who are intolerant of or have a contraindication to AChE inhibitors or people with severe AD. 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.

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

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Date searches conducted: 10/05/2012
Date answer completed: 21/05/2012

References

RCTs

1. Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, Burns A, Dening T, Findlay D, Holmes C, Hughes A, Jacoby R, Jones R, Jones R, McKeith I, Macharouthu A, O'Brien J, Passmore P, Sheehan B, Juszczak E, Katona C, Hills R, Knapp M, Ballard C, Brown R, Banerjee S, Onions C, Griffin M, Adams J, Gray R, Johnson T, Bentham P, Phillips P. *Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease.* The New England Journal of Medicine 2012; 366:893-903.

2. Modrego P, Fayedb N, Erreac J, Riosc C, Pinad M, Sarasae 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

Guidelines

3. Scottish Intercollegiate Guidelines Network. Guideline 86 Management of patients with dementia. Feb 2006. (http://www.sign.ac.uk/pdf/sign86.pdf)

4. 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

5. 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

Results

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Howard et al. (2012)	*Participants:* Patients with moderate-to-severe Alzheimer's disease (Standardized Mini–Mental State Examination (SMMSE 5-13)), who had been prescribed donepezil for at least three months prior to the start of the study with a dose of 10 mg for at least the previous six weeks, were eligible for inclusion. In addition, each patient's prescribing clinician had to be considering a change in treatment (i.e. stopping donepezil or introducing memantine). Patients were excluded if they had severe or unstable medical conditions, were receiving memantine, or were considered to be unlikely to adhere to the study regimens. *Interventions and comparisons:* Participants were randomly assigned to one of four treatment groups: 1. Discontinuation of donepezil (5 mg/d donepezil weeks 1-4 and placebo donepezil from week 5) +	N=295 randomised: Group 1 (donepezil discontinued and placebo memantine added) N=73 Group2 (donepezil discontinued and active memantine added) N=76 Group 3 (donepezil continued and placebo memantine added) N=73 Group 4 (donepezil continued and active memantine added) N=73	The four treatment groups were similar at baseline in terms of demographic characteristics, duration of previous treatment with donepezil, and symptom and quality of life scores. The article reports data on the mean difference, with 95% confidence intervals (CIs), between patients continuing and discontinuing donepezil (groups 3&4 versus groups 1&2) and between patients taking active and placebo memantine (groups 2&4 versus groups 1&3) for all outcome measures, at weeks 6, 18, 30 and 52. The authors reported that, from 6 weeks onward, the differences between the treatment groups were roughly parallel. 217 participants provided complete data (up to week 52) for both primary outcome measures. Average treatment effects over the 52 weeks were as follows: Patients who continued donepezil had higher SMMSE scores than those who discontinued (+1.9 points (95% CI: +1.3 to +2.5, P<0.001)), indicating better cognitive function. Baseline severity of dementia at significantly influenced the effect of donepezil on SMMSE; with moderate disease (SMMSE score, 10 to 13) the average difference between those continuing and discontinuing donepezil was +2.6 points (95% CI, +1.5 to +3.7) and in those with severe disease (SMMSE score, 5 to 9) the average was +1.3 points (95% CI, +0.2 to +2.4).	Treatment assignments were made (by telephone) by the U.K. Medical Research Council Clinical Trials Unit. Matched placebo tablets were provided by the manufacturers and patients, caregivers, clinicians, outcome assessors, and investigators were unaware of the

	placebo memantine starting in week 1. 2. Discontinuation of donepezil (5 mg/d donepezil weeks 1-4 and placebo donepezil from week 5) + 5 mg memantine starting in week 1 (dose increased in weekly 5 mg increments to 20 mg from week 4). 3. Continuation of 10mg/donepezil + placebo memantine, starting in week 1. 4. Continuation of 10 mg/d donepezil + 5 mg memantine starting in week 1 (dose increased in weekly 5 mg increments to 20 mg from week 4). *Outcomes:* The primary outcome measures were scores on the SMMSE and Bristol Activities of Daily Living Scale (BADLS). Secondary outcomes were scores on the Neuropsychiatric Inventory (NPI), the health-related quality of life measure for people with dementia DEMQOL-Proxy and caregiver health status assessed using General Health Questionnaire 12 (GHQ-12). The authors defined minimum clinically important differences as 1.4 points on the SMMSE and 3.5 points on the BADLS. *Duration:* 52 weeks' treatment		BADLS that were lower in patients who continued donepezil (-3.0 points (95% CI: -1.8 to -4.3, P<0.001)), indicating less functional impairment. There were no significant differences in NPI or caregiver GHQ-12 scores between patients who continued donepezil and those who discontinued. Results for DEMQOL-Proxy (patient quality of life) were not reported in the main article. Patients receiving memantine had higher SMMSE scores (+1.2 points (95% CI: +0.6 to +1.8, P<0.001)) and lower BADLS scores (-1.5 points (95% CI: -0.3 to -2.8, P = 0.02)) than those receiving placebo. However, these differences were smaller than the clinically important difference. Patients receiving memantine had lower NPI scores (-4.0 points (99% CI: -0.6 to -7.4, P = 0.002)) than those receiving placebo. There were no significant differences in caregiver GHQ-12 scores between patients who received memantine and those who received placebo. Results for DEMQOL-Proxy (patient quality of life) were not reported in the main article. There was no significant benefit of adding memantine to donepezil (group 4 versus group 3), with respect to SMMSE, BADLS, or NPI. Sensitivity analyses indicated no significant effects on results of treatment withdrawal and missing outcome assessments. There was no evidence that the incidence of serious adverse events or death differed according to treatment group.	treatment assignments. Data from participants were analyzed according to the groups to which they had been assigned, and all patients who received at least one dose of the study drug were included in the analyses. The primary outcomes and most secondary outcomes were fully reported, however, data on patient quality of life

				(DEMQOL-Proxy) were missing from the main article.
Modrego et al (2010)	*Participants:* Patients with mild to moderate Alzheimer's disease (either: MMSE of over 15, in the Spanish version of the rating scale, where upper limit is 35, or stage one or two of the Clinical Dementia Rating Scale). Patients with dementia other than AD, psychotic disorder, lack of reliable caregiver, current systemic illness influencing cognitive assessment, pacemaker, or history of previous treatment with cholinesterase inhbitors or memantine were excluded. *Intervention:* Memantine hydrochloride 20mg daily (with appropriate dose escalation), withdrawn 48 hours before clinical examination. *Comparisons:* Donepezil hydrochloride initially administered at 5mg daily reaching a dose of 10mg at 1 month, withdrawn 48 hours before clinical examination. *Outcomes:*	N= 67 randomised N= 63 completed trial and included in analyses (n=31 memantine, n=32 donepezil)	This article reports data on mean (SD) change from baseline to 24 weeks in the ADAS-Cog, NPI and DAD. The mean baseline scores for Mini-Examen Cognoscitivo (MEC), ADAScog, NPI, and DAD were similar for the two treatment groups. There were no significant differences in the change from baseline between donepezil and memantine for any outcome measure. For the donepezil group, there was deterioration from baseline in all measures. However, this deterioration only reached statistical significance for DAD 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. For the memantine group there was a deterioration from baseline in ADAS-Cog and DAD scores, and improvement in NPI score. None of these changes were statistically significant. Change from baseline in the ratio of N-acetylaspartate (NAA), a marker of neuronal density, to creatine in the posterior cingulate gyrus were correlated with changes in ADAS-cog (r = -0.36; P = 0.004). None of the baseline metabolite levels predicted response to treatment in any of the areas of the brain examined. Three patients on memantine were changed to donepezil because of headache and irritability, and one on donepezil to memantine because of gastric disturbances.	The article reported the trial to be 'rater-blinded' but did not report it to be double-blind. Patients who did not complete the study were excluded from the analyses. However, excluded participants represented <10% of the total study population, and this was therefore less likely to have affected results. The method

	Outcomes assessed were change from baseline to six months in the Alzheimer's Disease Assessment Scale cognitive domain (ADAS-cog), neuropsychiatric inventory (NPI), and disability assessment for dementia (DAD). Changes from baseline in metabolite levels on ^{1}H magnetic resonance spectroscopy (MRS) in several areas of the brain were also reported. *Duration:* Twenty four weeks treatment.			used to generate the allocation sequence is not reported.

Risk of Bias: SRs

RCTs

Study	RISK OF BIAS					
	Random allocation	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective Reporting**
Howard 2012	☺	☺	☺	☺	☺	☹
Modrego 2010	☺	?	?	☺	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Dementia AND cholinesterase AND memantine	10	3
DARE	1 MeSH DESCRIPTOR Alzheimer Disease EXPLODE ALL TREES 215 2 MeSH DESCRIPTOR Dementia EXPLODE ALL TREES 380 3 MeSH DESCRIPTOR Delirium, Dementia, Amnestic, Cognitive Disorders EXPLODE ALL TREES 516 4 MeSH DESCRIPTOR Dementia, Vascular EXPLODE ALL TREES 14 5 MeSH DESCRIPTOR Lewy Body Disease EXPLODE ALL TREES 1 6 (dement*) IN DARE 388 7 (alzheimer* OR ADD OR AD) IN DARE 667 8 (parkinson*) IN DARE 202 9 MeSH DESCRIPTOR Cholinesterase Inhibitors EXPLODE ALL TREES 77 10 MeSH DESCRIPTOR Galantamine EXPLODE ALL TREES 23 11 MeSH DESCRIPTOR Memantine EXPLODE ALL TREES 29 12 cholinesterase adj inhibitor* 112 13 acetylcholinesterase adj inhibitor* 31 14 donepezil* 93 15 galantamin* 59 16 memantin* 45 17 rivastigmin* 61	157	0

	18 tacrin* 23 19 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 1333 20 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 181 21 #19 AND #20 157		
Primary studies			
CENTRAL	#1 (dementia):ti,ab,kw or (alzheimer*):ti,ab,kw 6752 edit delete #2 MeSH descriptor Alzheimer Disease, this term only 1893 edit delete #3 (#1 OR #2) 6752 edit delete #4 (cholinesterase):ti,ab,kw or (rivastigmine):ti,ab,kw or (donepezil):ti,ab,kw or (galantamine):ti,ab,kw 1808 edit delete #5 MeSH descriptor Cholinesterase Inhibitors explode all trees 765 edit delete #6 (#4 OR #5) 1808 edit delete #7 MeSH descriptor Memantine explode all trees 149 edit delete #8 (memantine):ti,ab,kw 319 edit delete #9 (#7 OR #8) 319 edit delete #10 (#3 AND #6 AND #9) 35 edit delete	35	2
PsycINFO	1. PsycINFO; alzheimer*.ti,ab; 33020 results. 2. PsycINFO; dementia.ti,ab; 36593 results. 3. PsycINFO; exp DEMENTIA/; 44334 results. 4. PsycINFO; ALZHEIMER'S DISEASE/; 26720 results. 5. PsycINFO; 1 OR 2 OR 3 OR 4; 57072 results. 6. PsycINFO; cholinesterase.ti,ab; 1675 results. 7. PsycINFO; CHOLINESTERASE INHIBITORS/; 1366 results. 8. PsycINFO; ChEI.ti,ab; 96 results.	97	

	9. PsycINFO; rivastigmine.ti,ab; 468 results. 10. PsycINFO; donepezil.ti,ab; 1007 results. 11. PsycINFO; (galantamine OR galanthamine).ti,ab; 476 results. 12. PsycINFO; 6 OR 7 OR 8 OR 9 OR 10 OR 11; 3052 results. 13. PsycINFO; memantine.ti,ab; 736 results. 14. PsycINFO; 5 AND 12 AND 13; 212 results. 15. PsycINFO; CLINICAL TRIALS/; 6016 results. 16. PsycINFO; random*.ti,ab; 108705 results. 17. PsycINFO; groups*.ti,ab; 323490 results. 18. PsycINFO; (doubl* adj3 blind*).ti,ab; 16279 results. 19. PsycINFO; (singl* adj3 blind*).ti,ab; 1339 results. 20. PsycINFO; EXPERIMENTAL DESIGN/; 8214 results. 21. PsycINFO; controlled.ti,ab; 67972 results. 22. PsycINFO; (clinical adj3 study).ti,ab; 6773 results. 23. PsycINFO; trial.ti,ab; 57237 results. 24. PsycINFO; "treatment outcome clinical trial".md; 21794 results. 25. PsycINFO; 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24; 496443 results. 26. PsycINFO; 14 AND 25; 97 results.		
MEDLINE	18. MEDLINE; ALZHEIMER'S DISEASE/; 58193 results. 19. MEDLINE; 15 OR 16 OR 17 OR 18; 140909 results. 20. MEDLINE; cholinesterase.ti,ab; 13173 results. 21. MEDLINE; CHOLINESTERASE INHIBITORS/; 15473 results. 22. MEDLINE; ChEI.ti,ab; 165 results. 23. MEDLINE; rivastigmine.ti,ab; 958 results. 24. MEDLINE; donepezil.ti,ab; 1850 results. 25. MEDLINE; (galantamine OR galanthamine).ti,ab; 1235 results. 26. MEDLINE; 20 OR 21 OR 22 OR 23 OR 24 OR 25;	153	

	25528 results. 27. MEDLINE; memantine.ti,ab; 1694 results. 28. MEDLINE; 19 AND 26 AND 27; 408 results. 39. MEDLINE; "randomized controlled trial".pt; 326996 results. 40. MEDLINE; "controlled clinical trial".pt; 84070 results. 41. MEDLINE; placebo.ab; 135830 results. 42. MEDLINE; random*.ab; 580037 results. 43. MEDLINE; trial.ti; 104347 results. 44. MEDLINE; CLINICAL TRIALS AS TOPIC/; 159870 results. 45. MEDLINE; 39 OR 40 OR 41 OR 42 OR 43 OR 44; 922043 results. 46. MEDLINE; exp ANIMALS/ NOT HUMANS/; 3712811 results. 47. MEDLINE; 8 NOT 9; 842713 results. 48. MEDLINE; 28 AND 47; 153 results.		
EMBASE	15. EMBASE; alzheimer*.ti,ab; 96326 results. 16. EMBASE; dementia.ti,ab; 73248 results. 17. EMBASE; exp DEMENTIA/; 189509 results. 18. EMBASE; ALZHEIMER'S DISEASE/; 103475 results. 19. EMBASE; 15 OR 16 OR 17 OR 18; 211907 results. 20. EMBASE; cholinesterase.ti,ab; 14164 results. 21. EMBASE; CHOLINESTERASE INHIBITORS/; 15775 results. 22. EMBASE; ChEI.ti,ab; 241 results. 23. EMBASE; rivastigmine.ti,ab; 1408 results. 24. EMBASE; donepezil.ti,ab; 2627 results. 25. EMBASE; (galantamine OR galanthamine).ti,ab; 1715 results. 26. EMBASE; 20 OR 21 OR 22 OR 23 OR 24 OR 25; 28139	249	

	results. 27. EMBASE; memantine.ti,ab; 2405 results. 28. EMBASE; 19 AND 26 AND 27; 732 results. 29. EMBASE; random*.tw; 722076 results. 30. EMBASE; factorial*.tw; 18697 results. 31. EMBASE; placebo*.tw; 173569 results. 32. EMBASE; (crossover* OR cross-over*).tw; 60681 results. 33. EMBASE; (doubl* adj3 blind*).tw; 127267 results. 34. EMBASE; (singl* adj3 blind*).tw; 13948 results. 35. EMBASE; assign*.tw; 201557 results. 36. EMBASE; allocat*.tw; 67476 results. 37. EMBASE; volunteer*.tw; 155036 results. 38. EMBASE; CROSSOVER PROCEDURE/; 33755 results. 39. EMBASE; DOUBLE-BLIND PROCEDURE/; 108636 results. 40. EMBASE; SINGLE-BLIND PROCEDURE/; 15834 results. 41. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 321249 results. 42. EMBASE; 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41; 1192918 results. 43. EMBASE; 28 AND 42; 249 results.		
Summary	**NA**	**NA**	

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