BEST in Mental Health

BEST.awp.nhs.uk

Best Evidence Summaries of Topics in Mental Healthcare

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

Question

For adults with Alzheimer's Disease, how effective is Donezepil compared with other medications or no medication, in improving all patient outcomes?

Clarification of question using *PICO* structure

Patients:	Adults with Alzheimer's Disease
Intervention:	Donezepil
Comparator:	Other medications or no medication
Outcome:	All patient outcomes

Email: awp.BESTinMH@nhs.net Phone: 0117 378 4232/4233/4335 @BESTinMH

Clinical and research implications

Evidence from a systematic review, which included ten relevant randomised controlled trials, indicated that donezepil may have a small benefit for slowing decline in cognition, function, behaviour and clinical global change in patients with Alzheimer's disease. Both 5 mg/d and 10 mg/d doses appeared to be effective in patients with mild to moderate disease, however, evidence of effectiveness was restricted to the 10 mg/d dose in people with severe disease. The 10 mg/d dose, but not the 5 mg/d dose of donezepil, was associated with increased rates of adverse events and withdrawals.

All evidence was derived from placebo controlled trials; there were no studies providing direct comparisons of effectiveness between drugs. High quality studies comparing the effectiveness of different cholinesterase inhibitors and memantine are needed, as well as studies further investigating how effectiveness varies with disease severity.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified one systematic review which reported results relevant to this evidence summary. The review assessed the effectiveness of cholinesterase inhibitors and memantine for the management of people with Alzheimer's disease (AD) and included 23 studies, of which ten assessed the effectiveness of donezepil (5 mg/d or 10 mg/d). All studies included in the review were randomised, placebo-controlled trials; there were no direct comparisons of effectiveness between drugs. Three studies were conducted in people with severe AD, one in people with moderate to severe AD, four in people with mild to moderate/moderately severe AD, and one in people with mild AD; one study did not report details of disease severity. All studies lasted 24 weeks.

Main findings

Both doses of donezepil were associated with improvements in cognitive symptoms and clinical global impression, relative to placebo, in people with mild to moderate AD. Studies of behavioural symptoms and Activities of Daily Living (ADL) were conducted in people with severe or moderate-to-severe AD: 10 mg/d donezepil was associated with improvements in behavioural symptoms relative to placebo and 5 mg/d donezepil was not assessed by any study; 10 mg/d donezepil was associated with a small improvement in ADL relative to placebo, but 5 mg/d had no significant effect. Overall, the 10 mg/d dose of donezepil was generally associated with increased rates of adverse events and withdrawals relative to placebo, whereas the 5 mg/d dose was not.

Author's conclusions

Cholinesterase inhibitors, including Donezepil, were associated with modest overall benefits for slowing decline in cognition, function, behaviour and clinical global change of patients with Alzheimer's disease. Compared with placebo, more dropouts and adverse events occurred with the cholinesterase inhibitors.

Reliability of conclusions/Strength of evidence

The evidence included in this summary was derived from one systematic review, which included ten relevant randomised controlled trials. The review methods were poorly reported with respect to the

study selection, data extraction and quality assessment processes and it is therefore not possible to adequately assess the risk of bias in this review.

What do guidelines say?

The National Institute for Health and Care Excellence (NICE) guidelines, 'Donezepil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease' (2011), make the following comments on the effectiveness of donezepil compared with other medications or no medication, in improving all patient outcomes:

"4.1.5 For donepezil, the Assessment Group found no new studies reporting the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) at 12 or 24 weeks or MMSE at 12 weeks. The effectiveness estimates using these scales were therefore based on the studies included in NICE technology appraisal guidance 111. One new study was found that measured the effect of donepezil on cognition at 24 weeks follow-up. The overall pooled benefit using new and old data was significant on all scales (a mean change from baseline versus placebo of 1.165 [$p < 0.001$] and 1.206 [$p < 0.001$] at 12 and 24 weeks respectively using MMSE score, and -1.969 [$p = 0.006$] and -2.895 [$p < 0.001$] at 12 and 24 weeks respectively using ADAS-cog score) and the standardised mean difference of pooled outcomes increased with time for ADAS-cog. According to the manufacturer of donepezil, all 12 randomised controlled trials (from NICE technology appraisal guidance 111 and new submissions that reported on cognition using the ADAS-cog, MMSE or Severe Impairment Battery [SIB] scales) showed a statistically significant difference favouring donepezil versus placebo, with four of these reporting a statistically significant difference on two different cognitive scales. (p12)

4.1.8 …A submitted meta-analysis of ten trials also showed significant improvement in global function compared with placebo using the [clinical dementia rating; (CDR)]" (p13)

4.1.30 The Assessment Group identified four head-to-head randomised controlled trials (two comparing all three AChE inhibitors, one comparing donepezil with rivastigmine and one comparing donepezil with galantamine) but considered only one of the studies to be of sufficiently high quality to inform this review. The included study (which compared donepezil with rivastigmine) noted that over 2 years there was no statistically significant difference between rivastigmine and donepezil for cognitive outcomes (MMSE and SIB). Patients taking rivastigmine had significantly improved outcomes than those taking donepezil in the primary analysis of functional outcomes ($p = 0.007–0.047$). No significant difference was seen between donepezil and rivastigmine for behavioural outcomes (NPI). The study showed that patients taking rivastigmine did significantly better than those taking donepezil in terms of global outcomes (GDS). only one of the studies to be of sufficiently high quality to inform this review.

The included study (which compared donepezil with rivastigmine) noted that over 2 years there was no statistically significant difference between rivastigmine and donepezil for cognitive outcomes (MMSE and SIB). Patients taking rivastigmine had significantly improved outcomes than those taking donepezil in the primary analysis of functional outcomes ($p = 0.007–0.047$). No significant difference was seen between donepezil and rivastigmine for behavioural outcomes (NPI). The study showed that patients taking rivastigmine did significantly better than those taking donepezil in terms of global outcomes (GDS)." (p19)

The evidence included in this summary is consistent with current guidance.

Date question received: 03/07/2015
Date searches conducted: 14/07/2015
Date answer completed: 27/07/2015

References

Systematic reviews

Tan, C. C., Yua, J. T., Wangb, H. F., Tanc, M. S., Menga, X. F., & Wanga, C. (2014). Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Journal of Alzheimer's Disease*, *14*, 15.

Guidelines

The National Institute for Health and Care Excellence (2011). *Donezepil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease* , NICE Technology Appraisal Guidance 217. Retrieved at: http://www.nice.org.uk/guidance/ta217/resources/guidance-donepezil-galantamine-rivastigmine-and-memantine-for-the-treatment-of-alzheimers-disease-pdf

Results

Systematic reviews

Author (year)	Search date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Tan et al. (2014)	11/2013	*Participants*: Patients with probable or possible Alzheimer's Disease (AD) (according to the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV)) and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). *Intervention*: Cholinesterase inhibitor (donepezil, galantamine, rivastigmine) or memantine. Ten studies investigated donezepil; 4 studies used a fixed dose of 5mg (per day), 5 studies used a fixed dose of 10mg; 3 adopted a flexible dose regimen, ranging between 5 and 10mg. All studies lasted 24 weeks. *Comparator*: Placebo *Outcome*: (i) Cognitive function (in 4 studies), measured by	23 (10 studies on Donepezil)	This systematic review aimed to assess the efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease. All of the studies included in the review were placebo controlled trials; there were no direct comparisons between treatments. Ten of the 23 studies included in the review assessed the effectiveness of donezepil. Baseline participant caharcateristics (age, gender and MMSE score) were similar in the treatment and placebo groups. Nine studies assessed 10 mg/d donezepil and four studies assessed 5 mg/d (three studies assessed both doses). Seven studies used fixed doses of donezepil and three had flexible dosing regimens. Three studies were conducted in people with severe AD, one in people with moderate to severe AD, four in people with mild to moderate/moderately severe AD, and one in people with mild AD; one study	The research objective was clearly stated and appropriate inclusion criteria were defined. A range of bibliographic databases and conference proceedings were searched and search terms were reported. No details of the processes of study selection and data extraction, or the numbers of reviewers involved

		the Alzheimer's Disease Assessment Scale (ADAS-cog); (ii) Global assessment (in 5 studies), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS/ADL); (iii) Behavioural symptoms (in 3 studies), measured by the Neuropsychiatric Inventory (NPI); (iv) Functional outcome (in 3 studies), measured by the ADCS/ADL; (v) Safety and tolerability (in all 10 studies), including dropout rates. *Study design*: Double-blind parallel-group randomised controlled trials (RCTs), with at least 20 weeks treatment duration.		did not report details of disease severity. All studies had a duration of 24 weeks. *Cognitive function:* Donezepil was associated with greater reductions in cognitive impairment (ADAS-cog) than placebo, at both 5 mg/d and 10 mg/d doses: weighted mean difference (WMD) -1.95 (95% CI: -2.60 to -1.29), 3 studies in people with mild to moderate AD; WMD -2.48 (95% CI: -3.23 to -1.73), 4 studies (3 in people with mild to moderate AD and 1 in people with mild AD). *Global assessment:* Donezepil was associated with higher numbers of participants with improvements on the Clinicians' Global Impression of Change scale (CIBIC+) than placebo, at both 5 mg/d and 10 mg/d doses: Risk ratio (RR) 1.55 (95% CI: 1.19 to 2.00), 3 studies in people with mild to moderate AD; RR 1.66 (95% CI: 1.38 to 2.00), 5 studies (4 in people with mild to moderate AD and 1 in people with severe AD). No sensitivity analyses were reported, however, the study conducted in people with severe AD showed no statistically significant treatment effect,	were reported. A brief description of randomisation and analysis methods was provided (no details for individual studies), but no formal methodological quality assessment was described. The methods used to blind study participants (treatments matched on appearance) were also described and erroneously reported as allocation concealment. The review authors stated that "studies with fatal flaws in study design or data analysis were

				Behavioural symptoms: Three studies assessed the effect of 10 mg/d donezepil on behavioural symptoms measured by the Neuropsychiatric Inventory (NPI) scale. One study was conducted in people with severe AD, one in people with moderate to severe AD and one did not report disease severity. Results of meta-analysis indicated that donezepil was associated with greater reductions in behavioural symptoms than placebo: WMD -2.72 (95% CI: -4.92 to -0.52), however, statistical heterogeneity was high. *Functional outcome:* Three studies assessed the effects of donezepil on Activities of Daily Living (ADCS/ADL); all were conducted in people with severe AD. One study assessed 5 mg/d donezepil and found no significant treatment effect. Meta-analysis indicated that 10 mg/d donezepil was associated with a small improvement in ADL compared to placebo: WMD 1.03 (95% CI: 0.21 to 1.85), 3 studies. *Safety and tolerability:* There was no significant difference in the number of all cause withdrawals between 5	excluded," but did not provide any further details. Meta-analyses used a fixed effect model. This was broadly appropriate as, although there were high levels of statistical heterogeneity in some analyses the numbers of studies were frequently too small to support a random effects model. Analyses were stratified by treatment dose. Sensitivity analyses were used to investigate the possible effects of disease severity, for galantamine and functional

				mg/d donezepil and placebo: RR 0.91 (95% CI: 0.71 to 1.17), 3 studies. However, all cause withdrawal rates were higher for 10 mg/d donezepil than for placebo: RR 1.31 (95% CI: 1.12 to 1.53), 8 studies. Results were similar for withdrawals caused by adverse events. For specific adverse events, there were no significant differences between 5 mg/d donazepil and placebo in the rates of nausea, vomiting, anorexia, dizziness, or headache; donezepil was associated with increased risk of diarrhoea. By contrast, 10 mg/d donezepil was associated with an increased risk of all specified adverse events except headache.	outcome.

Risk of bias

Systematic reviews

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review process	Quality assessment	Synthesis
Tan 2014	☺	☺	?	?	☺

☺ Low risk ☹ High risk ? Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
Guidelines			
NICE	donepezil alzheimer	9	1
Systematic Reviews			
MEDLINE	1. Medline; (Donepezil OR Aricept).ti,ab; 2424 results. 2. Medline; exp ALZHEIMER DISEASE/; 69431 results. 3. Medline; Alzheimer*.ti,ab; 96660 results. 4. Medline; 2 OR 3; 107121 results. 5. Medline; 1 AND 4; 1636 results. 6. Medline; ((("systematic* review*") OR meta-analytic* OR metanalysis OR metaanalysis OR ("meta analysis") OR meta-synthesis OR metasynthesis OR ("meta synthesis") OR meta-regression OR metaregression OR ("meta regression") OR (synthes* adj3 literature) OR (synthes* adj3 evidence) OR ("integrative review") OR ("data synthesis") OR ("research synthesis") OR ("narrative synthesis") OR ("systematic study") OR ("systematic studies"))).ti,ab; 129153 results. 7. Medline; META-ANALYSIS AS TOPIC/; 14045 results. 8. Medline; meta-analysis.ti,ab,pt; 81638 results. 9. Medline; ((("systematic comparison*") OR ("systematic overview*") OR ("evidence based review") OR ("comprehensive review") OR ("critical review") OR ("quantitative review") OR ("structured review") OR ("realist review") OR ("realist synthesis"))).ti,ab; 23752 results. 10. Medline; 6 OR 7 OR 8 OR 9; 170095 results. 11. Medline; ((medline OR pubmed OR cochrane OR embase OR cinahl OR psyclit OR psycinfo OR psychlit OR psychinfo OR (literature adj3 search*) OR (database* adj3 search*) OR (bibliographic adj3 search*) OR (electronic adj3 search*) OR (electronic adj3 database*) OR (computerized adj3 search*) OR (computerised adj3 search*) OR (internet adj3 search*) OR ("included studies") OR ("inclusion studies") OR ("inclusion criteria") OR ("selection criteria") OR ("selection criteria") OR ("predetermined criteria"))).ti,ab; 183675 results. 12. Medline; ((medline OR pubmed OR cochrane OR embase OR cinahl OR psyclit OR psycinfo OR psychlit OR	81	1

	psychinfo OR (literature adj3 search*) OR (database* adj3 search*) OR (bibliographic adj3 search*) OR (electronic adj3 search*) OR (electronic adj3 database*) OR (computerized adj3 search*) OR (computerised adj3 search*) OR (internet adj3 search*) OR ("included studies") OR ("inclusion studies") OR ("inclusion criteria") OR ("selection criteria") OR ("selection criteria") OR ("predetermined criteria"))).ab; 180865 results. 13. Medline; ((("predefined criteria") OR (assess* adj3 (quality OR validity)) OR (select* adj3 (study OR studies)) OR (data adj3 extract*) OR ("extracted data") OR (data adj2 abstracted) OR (data adj3 abstraction) OR ("published intervention") OR ((study OR studies) adj2 evaluat*) OR (intervention* adj2 evaluat*) OR ("confidence interval") OR heterogeneity OR pooled OR pooling OR ("odds ratio*") OR Jadad OR coding)).ab; 921867 results. 14. Medline; 11 OR 12 OR 13; 1043858 results. 15. Medline; 10 AND 14; 91920 results. 16. Medline; review.ti; 285620 results. 17. Medline; 14 AND 16; 57910 results. 18. Medline; ((review* adj4 (papers OR trials OR studies OR evidence OR intervention* OR evaluation*))).ti,ab; 134956 results. 19. Medline; 10 OR 15 OR 17 OR 18; 277206 results. 20. Medline; (letter OR editorial OR comment).pt; 1404081 results. 21. Medline; exp ANIMALS/; 17905365 results. 22. Medline; exp HUMANS/; 13884983 results. 23. Medline; 21 NOT 22; 4020382 results. 24. Medline; 20 OR 23; 5370109 results. 25. Medline; 19 NOT 24; 260123 results. 26. Medline; 25 [Limit to: Publication Year 2006-2015]; 181386 results. 27. Medline; 5 AND 26 [Limit to: Publication Year 2006-2015]; 81 results.		
EMBASE	1. EMBASE; (Donepezil OR Aricept).ti,ab; 3673 results. 2. EMBASE; exp ALZHEIMER DISEASE/; 135974 results. 3. EMBASE; Alzheimer*.ti,ab; 129801 results. 4. EMBASE; 2 OR 3; 159530 results. 5. EMBASE; 1 AND 4; 2518 results. 6. EMBASE; 5 [Limit to: (EBM-Evidence Based Medicine Meta Analysis or Systematic Review)]; 130 results.	80	1

	7. EMBASE; 6 [Limit to: (EBM-Evidence Based Medicine Meta Analysis or Systematic Review) and Publication Year 2006-2015]; 80 results.		
PsycINFO	1. PsycInfo; (Donepezil OR Aricept).ti,ab; 1227 results. 2. PsycInfo; exp ALZHEIMER DISEASE/; 2318 results. 3. PsycInfo; Alzheimer*.ti,ab; 43687 results. 4. PsycInfo; 2 OR 3; 43766 results. 5. PsycInfo; 1 AND 4; 798 results. 6. PsycInfo; ((systematic* adj1 review*) OR meta-analytic* OR metanalysis OR metaanalysis OR (meta adj1 analysis) OR meta-synthesis OR metasynthesis OR (meta adj1 synthesis) OR meta-regression OR . AND metaregression OR (meta adj1 regression) OR (synthes* adj3 literature) OR (synthes* adj3 evidence) OR (integrative adj1 review) OR (data adj1 synthesis) OR (research adj1 synthesis) OR (narrative adj1 synthesis) OR (systematic adj1 study) OR (systematic adj1 studies)).ti,ab; 37460 results. 7. PsycInfo; meta-analysis.ti,ab,pt; 16118 results. 8. PsycInfo; ((systematic adj1 comparison*) OR (systematic adj1 overview*) OR (evidence based review) OR (comprehensive adj1 review) OR (critical adj1 review) OR (quantitative adj1 review) OR (structured adj1 review) OR (realist adj1 review) OR (realist adj1 synthesis)).ti,ab; 22471 results. 9. PsycInfo; 6 OR 2 OR 7 OR 8; 56286 results. 10. PsycInfo; review.pt; 115062 results. 11. PsycInfo; (medline OR pubmed OR cochrane OR embase OR cinahl OR psyclit OR psycinfo OR psychlit OR psychinfo OR (literature adj3 search*) OR (database* adj3 search*) OR (bibliographic adj3 search*) OR (electronic adj3 search*) OR (electronic adj3 database*) OR (computerized adj3 search*) OR (computerised adj3 search*) OR (internet adj3 search*) OR (included adj1 studies) OR (inclusion adj3 studies) OR (inclusion adj1 criteria) OR (selection adj1 criteria) OR (selection adj1 criteria) OR (predetermined criteria)).ab; 3653167 results. 12. PsycInfo; ((predefined adj1 criteria) OR (assess* adj3 (quality OR validity)) OR (select* adj3 (study OR studies)) OR (data adj3 extract*) OR (extracted adj1 data) OR (data adj2 abstracted) OR (data adj3 abstraction) OR (published adj1 intervention) OR ((study OR studies) adj2 evaluat*) OR (intervention* adj2 evaluat*) OR (confidence adj1 interval) OR heterogeneity OR pooled OR pooling OR (odds adj1 ratio*) OR Jadad OR coding).ab; 131412 results. 13. PsycInfo; 10 OR 11 OR 12; 3653167 results. 14. PsycInfo; 9 AND 13; 55958 results.	35	0

	15. PsycInfo; review.ti; 122999 results. 16. PsycInfo; 13 AND 15; 122468 results. 17. PsycInfo; ((review* adj4 (papers OR trials OR studies OR evidence OR intervention* OR evaluation*))).ti,ab; 52677 results. 18. PsycInfo; 9 OR 14 OR 16 OR 17; 192131 results. 19. PsycInfo; (letter OR editorial OR comment).pt; 156316 results. 20. PsycInfo; exp ANIMALS/; 6773 results. 21. PsycInfo; exp HUMANS/; 1795 results. 22. PsycInfo; 20 NOT 21; 6460 results. 23. PsycInfo; 19 OR 22; 162445 results. 24. PsycInfo; 18 NOT 23; 185104 results. 25. PsycInfo; META ANALYSIS/; 14573 results. 26. PsycInfo; 24 OR 25; 186607 results. 27. PsycInfo; 26 [Limit to: Publication Year 2006-2015]; 100970 results. 28. PsycInfo; 5 AND 27 [Limit to: Publication Year 2006-2015]; 35 results.		
Primary Studies			
MEDLINE	2. Medline; exp ALZHEIMER DISEASE/; 69431 results. 3. Medline; Alzheimer*.ti,ab; 96660 results. 4. Medline; 2 OR 3; 107121 results. 5. Medline; (Donepezil OR Aricept).ti; 1218 results. 6. Medline; 4 AND 5; 797 results. 7. Medline; RANDOMIZED CONTROLLED TRIALS AS TOPIC/; 96724 results. 8. Medline; RANDOMIZED CONTROLLED TRIAL/; 0 results. 9. Medline; RANDOM ALLOCATION/; 83082 results. 10. Medline; DOUBLE-BLIND METHOD/; 128910 results. 11. Medline; SINGLE-BLIND METHOD/; 20353 results. 12. Medline; CLINICAL TRIAL/; 0 results. 13. Medline; CLINICAL TRIAL, PHASE I/ OR CLINICAL TRIAL, PHASE II/ OR CLINICAL TRIAL, PHASE III/ OR CLINICAL TRIAL, PHASE IV/; 0 results. 14. Medline; CONTROLLED CLINICAL TRIAL/; 0 results. 15. Medline; MULTICENTER STUDY/; 0 results.	151	0

	16. Medline; CLINICAL TRIALS AS TOPIC/; 171918 results. 17. Medline; 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16; 454855 results. 18. Medline; ((clinical ADJ trial*) OR ((singl* OR doubl* OR treb* OR tripl*) adj3 (blind* OR mask*)) OR placebo* OR (randomly adj1 allocated) OR (allocated adj2 random*)).ti,ab; 434603 results. 19. Medline; PLACEBOS/; 32647 results. 20. Medline; 18 OR 19; 445592 results. 21. Medline; 17 OR 20; 701837 results. 22. Medline; 6 AND 21; 297 results. 23. Medline; 22 [Limit to: Publication Year 2006-2015]; 151 results		
EMBASE	1. EMBASE; (Donepezil OR Aricept).ti,ab; 3673 results. 2. EMBASE; exp ALZHEIMER DISEASE/; 135974 results. 3. EMBASE; Alzheimer*.ti,ab; 129801 results. 4. EMBASE; 2 OR 3; 159530 results. 5. EMBASE; 1 AND 4; 2518 results. 6. EMBASE; 5 [Limit to: (Clinical Trials Randomized Controlled Trial) and Publication Year 2006-2015]; 161 results.		
CENTRAL	#1 (Donepezil or Aricept) 1013 #2MeSH descriptor: [Alzheimer Disease] 2261 #3 #1 and #2 269 Central only 180	180	0

Disclaimer

BEST in MH answers to clinical questions are for information purposes only. BEST in MH does not make recommendations. Individual health care providers are responsible for assessing the applicability of BEST in MH answers to their clinical practice. BEST in MH is not responsible or liable for, directly or indirectly, any form of damage resulting from the use/misuse of information contained in or implied by these documents. Links to other sites are provided for information purposes only. BEST in MH cannot accept responsibility for the content of linked sites.