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

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

Question

"In adults with Alzheimer's Disease or mixed dementia, which is the most effective Acetylcholinesterase Inhibitor in ameliorating symptoms or slowing deterioration in memory/cognition?"

Clarification of question using PICO structure

Patients: In adults with Alzheimer's Disease
Intervention: Any Acetylcholinesterase inhibitor
Comparator: Any other acetylcholinesterase inhibitor or placebo
Outcome: Ameliorating symptoms or slowing deterioration in memory/cognition

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Clinical and research implications

No definite clinical implications can be made from the available evidence. In order to best address the above question, head-to-head trials of acetylcholinesterase inhibitors are required, yet very few good quality head-to-head studies have been conducted (as reported by one well-conducted systematic review). Based on pairwise comparisons, there is some evidence to suggest that donepezil, rivastigmine and galantamine are all significantly more effective than placebo for cognitive outcomes.

The authors of a SR suggested that more good quality RCTs of long-term duration are required, and that trials should aim to use the same standardised outcomes measures. In addition, they stated that more research into valid ways of accounting for missing data are needed in studies that measure degenerative diseases such as AD.

What does the evidence say?

Number of included studies/reviews (number of participants)

One systematic review (SR), published as a Health Technology Assessment Report, met the inclusion criteria for this BEST summary (Bond et al. 2012). The review updated NICE guidance on the clinical effectiveness and cost-effectiveness of donepezil, galantamine and rivastigmine for mild-to-moderate Alzheimer's disease (AD), and memantine for moderate-to-severe AD. As such, data from both reviews (the old and new updated review) were synthesised where possible. We note that the search strategy for the update review was conducted in November 2009 and updated in March 2010.

Main Findings

The majority of studies included in this HTA review compared AChEIs with placebo. Meta-analyses showed that donepezil, rivastigmine (at a higher dose) and galantamine were all significantly more effective than placebo for cognitive outcomes. The SR also reported on four new head-to-head comparisons of AChEIs, yet only one of these studies evaluated cognition as an outcome (Bullock et al. 2005). In this well-conducted randomised study, a similar cognitive and behaviour decline was seen in individuals treated with donepezil compared with those treated with rivastigmine. Significant differences, were however, found for functional and global outcomes, both favouring rivatigmine. Three small head-to-head studies from the previous review indicated that there was no difference between donepezil and galantamine on cognitive outcomes.

The authors of the SR also conducted indirect analyses of the data. They reported that results for cognitive outcomes varied with follow-up time and the measure used. Donepezil was shown to be probably the most effective treatment at short-term follow-up on the ADAS-cog and MMSE (i.e. 12-16 weeks or 12-13 weeks), and for the MMSE at 24–26 weeks. Galantamine was, however, found to be most effective for ADAS-cog at longer-term follow-up.

Authors Conclusions

The authors concluded that additional clinical effectiveness evidence identified in this update systematic review continues to suggest clinical benefit from the AChEIs in alleviating AD symptoms, although there is considerable debate about the magnitude of the effect. There is also some evidence that AChEIs have an impact on controlling disease progression. Given the amount of

uncertainty in the mixed treatment results, it is impossible to say whether or not one AChEI is better than another at treating AD.

Reliability of conclusions/Strength of evidence
This was a well-conducted systematic review, although the quality of the included studies were considered to be moderate to poor by the study authors. The authors' appropriately stated that the lack of quality adds to the uncertainty of the results.

What do guidelines say?

NICE technology appraisal (TA127) regarding the use of acetylcholinesterase inhibitors for Alzheimer's disease states the following;

"The Committee considered whether there was evidence that one of the AChE inhibitors was more clinically effective than any other. The Committee noted that only one good-quality head-to-head randomised controlled trial comparing donepezil and rivastigmine had been published since 2004 and that this did not change the conclusions made in NICE technology appraisal guidance 111. The Committee concluded that there was insufficient evidence to differentiate between the AChE inhibitors in terms of clinical effectiveness." (pp.49)

Date question received: 24/12/2013
Date searches conducted: 02/01/2014
Date answer completed: 16/01/2013

References

SRs
Bond, M., Rogers, G., Peters, J., Anderson, R., Hoyle, M., Miners, A., Moxham, T., Davis, S., Thokala, P., Wailoo, A., Jeffreys, M. and Hyde, C. (2012) The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 11): a systematic review and economic model. *Health Technology Assessment 16* (**21**).

Guidelines
National Institute for Health and Care Excellence (2011) Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease.TA217. London: National Institute for Health and Care Excellence.
http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Bond et al. (2012)	11/2009 updated 03/2010	P: Systematic review that evaluated adults with Alzheimer's disease or mixed dementia with a MMSE score that did not exceed a mean baseline ±0.8416 standard deviation. I: Donepezil, galantamine, rivastigmine or memantine. C: Placebo, treatment without AChEIs or another AChEI. O: Cost effectiveness and clinical effectiveness; measures of severity and response to treatment, behavioural symptoms, mortality, ability to remain independent, likelihood of admission to residential/nursing care, HRQoL of patients and carers, adverse events of treatment. S: Systematic reviews of RCTS, and RCTs, were eligible for inclusion.	4 SRs and 17 RCTs (data from these studies were also summarised [in a meta-analysis] with those studies included in the previous review)	Of the 4 drugs evaluated in this SR, three are AChEIs and are of relevance to this BEST summary: donepezil, rivastigmine and galantamine (i.e. data on memantine have not been data extracted). *Systematic review evidence* One included SR (Birks et al. 2009) compared rivastigmine with placebo (no SRs were found that compared donepezil or galantamine with placebo). The SR by Birks reported that the use of rivastigmine (6–12 mg daily) was associated with a two-point improvement on the ADAS-cog compared with placebo [ITT WMD –1.99 (95% CI –2.49 to –1.50)] and a 2.2-point improvement on the Progressive Deterioration Scale (PDS) for ADL [ITT WMD –2.15 (95% CI –3.16 to –1.13)] at 26 weeks. The main AEs were gastrointestinal (nausea and vomiting), usually occurring during the titration phase. The authors concluded that rivastigmine provided a benefit to people with mild-to-	Low

				moderate AD when compared with placebo. In addition to the SRs, there were 12 pair-wise comparisons with placebo (donepezil 5, n = 234; galantamine 3, n = 1386; rivastigmine 3, n = 1995; and memantine 1, n = 350); four head-to-head studies and one combination therapy study (memantine added to AChEIs). *Randomised controlled trials* **Donepezil vs. placebo**: Pooled analysis demonstrated significant effects in favour of donepezil for cognition. **Galantamine vs. placebo**: When the results from studies were pooled with 2004 evidence, significant gains for people taking galantamine were found for cognitive, functional and global outcomes. **Rivastigmine vs. placebo**: Positive benefits for rivastigmine were found on cognitive, functional and global outcomes, but not on behavioural outcomes. The outcomes for rivastigmine were, however, found to be dose dependent. Four new head-to-head studies were found. Only one of the new studies was large and of reasonable quality; this compared donepezil to rivastigmine. It measured cognitive,	

				functional, behavioural and global outcomes, but found statistically significant differences only on functional and global outcomes, both favouring rivastigmine (i.e. there was no difference between treatment groups in cognition). Another new study compared donepezil with galantamine, and two compared all three AChEIs. Cognitive outcomes were, however, not reported in these latter three studies. Overall, three small head-to-head studies from the previous review indicated that there was no difference between donepezil and galantamine on cognitive outcomes. *Indirect analysis* The mixed treatment comparison (MTC) results for cognitive outcomes varied with follow-up time and the measure used. Donepezil was shown to be probably the most effective treatment at short-term follow-up on the ADAS-cog and MMSE, and this remained the case for the MMSE at 24–26 weeks; however, the ADAS-cog favoured galantamine at this later follow-up time. Functional outcomes measured with the ADCS-ADL showed equal effectiveness from galantamine and rivastigmine at 12–16	

				weeks, but by 21–26 weeks galantamine was probably the most effective treatment. For behavioural outcomes donepezil came out most favourably. For global outcomes the results were less clear, with galantamine probably the best treatment at 12–16 weeks when measured by the CIBIC-plus, but donepezil taking over by 24–28 weeks. However, when global outcomes were measured with the GDS, rivastigmine came out as the most effective. Cost-effectiveness data were reported but have not been extracted.	

Risk of Bias: SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Bond et al. (2012)	☺	☺	☺	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
NICE	Alzheimer's Disease	27	1
DARE	(alzheimer*) IN DARE 332 Delete 2 MeSH DESCRIPTOR Alzheimer Disease EXPLODE ALL TREES 280 Delete 3 (donepezil OR E2020 OR aricept) IN DARE 59 Delete 4 (galantamin* OR galanthamin*) IN DARE 41 Delete 5 (reminyl) IN DARE 4 Delete 6 (rivastigmine) IN DARE 39 Delete 7 (exelon) IN DARE 4 Delete 8 ((ENA adj2 713) OR ENA-713) IN DARE 3 Delete 9 (cholinesterase*) IN DARE 93 Delete 10 MeSH DESCRIPTOR Cholinesterase Inhibitors EXPLODE ALL TREES 89 Delete 11 MeSH DESCRIPTOR Acetylcholinesterase EXPLODE ALL TREES 1 Delete 12 MeSH DESCRIPTOR Galantamine EXPLODE ALL TREES 26 Delete 13 #1 OR #2 453 Delete 14 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 156		

	Delete 15 #13 AND #14		
Summary	**NA**	**NA**	

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