Cholinesterase inhibitors for patients with Alzheimer’s disease: systematic review of randomised clinical trials

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BMJ 2005;331:321-327
doi:10.1136/bmj.331.7512.321

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Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials

Abstract

Objectives Pharmacological treatment of Alzheimer's disease focuses on correcting the cholinergic deficiency in the central nervous system with cholinesterase inhibitors. Three cholinesterase inhibitors are currently recommended: donepezil, rivastigmine, and galantamine. This review assessed the scientific evidence for the recommendation of these agents.

Data sources The terms "donepezil", "rivastigmine", and "galantamine", limited by "randomized-controlled-trials" were searched in Medline (1989-November 2004), Embase (1989-November 2004), and the Cochrane Database of Systematic Reviews without restriction for language.

Study selection All published, double blind, randomised controlled trials examining efficacy on the basis of clinical outcomes, in which treatment with donepezil, rivastigmine, or galantamine was compared with placebo in patients with Alzheimer's disease, were included. Each study was assessed independently, following a predefined checklist of criteria of methodological quality.

Results 22 trials met the inclusion criteria. Follow-up ranged from six weeks to three years. 12 of 14 studies measuring the cognitive outcome by means of the 70 point Alzheimer's disease assessment scale—cognitive subscale showed differences ranging from 1.5 points to 3.9 points in favour of the respective cholinesterase inhibitors. Benefits were also reported from all 12 trials that used the clinician's interview based impression of change scale with input from caregivers. Methodological assessment of all studies found considerable flaws—for example, multiple testing without correction for multiplicity or exclusion of patients after randomisation.

Conclusion Because of flawed methods and small clinical benefits, the scientific basis for recommendations of cholinesterase inhibitors for the treatment of Alzheimer's disease is questionable.

Introduction

Currently the three cholinesterase inhibitors donepezil, rivastigmine, and galantamine are widely recommended for clinical use. The National Institute for Clinical Excellence (NICE, now National Institute for Health and Clinical Excellence), for example, says in its guidance for treatment of Alzheimer's disease that the three drugs should be made available in the NHS as one component of the management of people with mild and moderate Alzheimer's disease. The American Academy of Neurology also recommends cholinesterase inhibitors, although the average benefit seems small. The rationale for these recommendations is that evidence from randomised controlled trials has shown that all three drugs have beneficial effects on cognitive and global outcome measures. However, cholinesterase inhibitors are not widely prescribed. In Germany, donepezil, rivastigmine, and galantamine account for 10% of all antidementia drugs prescribed in 2003. The gap between multiple recommendations of these agents and their lack of use in daily clinical practice prompted us to review all available randomised controlled trials. The objective of this review is to explore the scientific evidence for the clinical use of donepezil, rivastigmine, and galantamine.

Methods

We searched the terms "donepezil", "rivastigmine", and "galantamine", limited by "randomized-controlled-trials" in Medline (1989-November 2004), Embase (1989-November 2004), and the Cochrane Database of Systematic Reviews, without restriction for language. Additionally we checked the bibliographical data of all included publications for further studies. We included all papers presenting original data of randomised, double blind, placebo controlled trials with donepezil, rivastigmine, or galantamine in patients with Alzheimer's disease and excluded trials that did not examine clinical outcomes or focused on vascular dementia. As the aim of our review was to explore the scientific evidence for the clinical benefits claimed for cholinesterase inhibitors and not to compare the benefits of the various cholinesterase inhibitors with each other, we did not include head to head comparisons in the analysis. Three of the authors (HK, TZ, HPBB) read each of the studies that met the inclusion criteria and assessed them independently, following a predefined checklist of criteria of methodological quality that was partly related to the CONSORT statement (table A on bmj.com). Some items of the checklist relate to findings, others to the study design, but we considered all to be important for a comprehensive interpretation of the results. We discussed every trial in detail, and at the end of the discussion process a joint assessment of each trial was achieved.

Results

Our literature search yielded a total of 412 references, of which 19 publications met the inclusion criteria. In addition we reviewed the bibliographies of the identified studies and of all available reviews for further studies, which yielded three additional papers. We identified 12 original publications of randomised controlled trials on donepezil, five on rivastigmine, and five on galantamine. Table B on bmj.com shows the main characteristics and results of these 22 randomised controlled trials. The duration of treatment varied between six weeks and three years. The number of patients included per study varied.
between 271 and 978.28 All studies included patients with an established diagnosis of probable or possible Alzheimer's disease, according to the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer Disease and Related Disorders Association,27 with one exception where a DSM-IV diagnosis of dementia was used for inclusion.23 In eight of the 22 trials, one primary efficacy measurement was used.6–10 14 16 17 20 26. The remaining 14 trials combined several instruments to assess efficacy of treatment or performed multiple analyses by using the same instrument.

**Assessment tools used**

Fourteen of 22 trials used the Alzheimer's disease assessment scale—cognitive subscale (ADAS-cog)40 as the primary measure of efficacy.6–8 10–12 16–20 22–26 This is a psychometric scale consisting of 11 items that evaluate selected aspects of memory, orientation, attention, language, reasoning, and carrying out instructions. Its score ranges from 0 (no impairment) to 70 (very severe impairment). In 12 of the 14 trials that used the scale, significant differences between cholinesterase inhibitor and placebo groups were reported, always favouring the treatment groups.21 22 24 25 28 The mean differences between treatment and placebo groups ranged from 1.5 points to 3.9 points.

In 12 trials, the clinician's interview based impression of change scale with caregiver input (CIBIC-plus41) was used to assess efficacy.6–8 11 16–25 This instrument uses information obtained during an independent clinical interview to assess disease severity and progression. A blinded clinician conducts interviews with patient and caregiver. The severity of the disease is rated at baseline and at subsequent visits. Change from baseline is scored by using a 7 point Likert-type scale, in which 1 represents marked improvement, 4 no change, and 7 marked worsening. Only full scores from 1 to 7 are used.

The differences on the CIBIC-plus scale between intervention and control groups were calculated in various manners in the trial reports. In five trials, differences of mean values between groups were calculated.4 7 11 16–18 In all five trials, significant benefits of the cholinesterase inhibitor were found; differences ranged from 0.26 points to 0.54 points. Eleven trials compared proportions of patients with a benefit on the CIBIC-plus scale in each of the groups.6–8 11 16–25 "Benefit" was defined as scores from 1-3, or 1-4—that is, the cut-off point for "benefit" was defined in different ways in the various trials. In all 11 trials, significant differences were reported in at least one of the treatment groups compared with placebo—again favouring treatment with cholinesterase inhibitors. However, in five trials7 13 20 22 25 statistical significance vanished in all dose groups after multiplicity has been corrected for, or after considering exclusion of patients in a worst case scenario.

In 10 trials, other instruments were used to evaluate the primary end point(s). In the trial reported by Mohs et al,22 the primary end point was time in days to reach clinically evident functional decline. Donepezil extended the median time to clinically evident functional decline by five months compared with placebo. The AD2000 Collaborative Group26 used as primary end points entry to institutional care and progression of disability. No significant differences were seen in either primary end point.

Tariot et al28 used the neuropsychiatric inventory as their endpoint measure. No difference between the donepezil and placebo group was found. Holmes et al26 also used the neuropsychiatric inventory as their endpoint measure. The results show a negative effect of withdrawal of donepezil. Winblad et al29 used the Gottfries-Brane-Steen scale and found no difference between donepezil and placebo. In three trials4 16 17 efficacy of treatment was assessed by means of the clinical global impression of change (CGIC42) scale, which is similar to the CIBIC-plus scale. Agid et al23 reported a difference between the 6 mg rivastigmine and the control group, but significance was lost after correction for multiplicity. Rogers et al23 found no difference, whereas Homma et al24 found a significant difference favouring donepezil.

Corey-Bloom et al30 and Rösler et al31 used the progressive deterioration scale (PDS31) as their primary outcome measure. In both trials, significant differences favouring rivastigmine were reported. In the study by Rösler et al,31 significance was lost after correction for multiplicity.

**Methodological quality of the trials**

Assessment of methodological quality of the 22 randomised controlled trials brought to attention numerous shortcomings (tables 1 and 2). A common shortcoming is the use of several “primary end points without correction for multiple comparisons (see note in table 1). After correction, two of the five trials on rivastigmine do not show any significant benefit on primary endpoint measures any more.17 18

**Missing intention to treat analysis**

Another shortcoming is a missing intention to treat analysis, as in 15 of the 22 trials patients were excluded from analysis after randomisation (table 1, “Missing patients,”17 9 11 14 15 16 18 20 20–28). In four trials, the number of participants included in endpoint analyses in each group was not reported at all or only partially.17 9 15 25 Consequently, in these four trials the dimension of potential bias emerging through exclusion of patients cannot even be estimated. Depending on the results, exclusion of patients might become very important when mean differences are calculated between treatment groups, because exclusion of only a few patients with extreme results might change the average results considerably. Unfortunately no information is provided in the reports that would allow the reader to assess the impact of excluding patients after randomisation. Furthermore, the calculation of means might be misleading even if patients are not excluded—for example, if a small proportion of patients benefit largely from treatment, the mean value might indicate an improvement even if treatment is slightly harmful for most.

**Incomplete data**

The handling of incomplete data (dropouts) constitutes another important problem. In at least eight of the trials6–8 16 18 24 25–26 the last observation carried forward (LOCF) method was used to include dropouts into endpoint analyses. This means that the last evaluation before dropout is defined as the endpoint measure. Since Alzheimer's disease is a progressive illness, early discontinuation of treatment because of side effects will pretend to show a reduced progression of the disease in endpoint analyses using last observation carried forward. In five trials using this method,7 13 20 22 25 dropout rates tended to be considerably higher in the treatment groups, which must have biased the results substantially. But even if dropout rates are equal in treatment and placebo groups, knowledge of dropout time is important to estimate possible bias. However, the exact time of dropouts is reported in none of the trials.

**Different design and methodological flaws**

Three studies need to be discussed separately as their design or methodological flaws differ from most of the reviewed trials.
Table 1 Methodological shortcomings of 12 randomised controlled trials on donepezil

| Author and year | Dose | Imbalance of groups at baseline with regard to | % of missing patients in endpoint analyses—cholinesterase inhibitor (placebo)* | Missing information in publication | No correction for multiple comparisons† | Calculation of mean values may bias results | Missing information on blinding in report | Other shortcomings
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<td>Weight and height</td>
<td>CGIC—2 (0)</td>
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<td>ADAS-cog—no of patients at end point</td>
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<td>5 mg</td>
<td>ADAS-cog</td>
<td>ADAS-cog—7 (14) J-CGIC—2 (2)</td>
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<td>Weight</td>
<td>Not reported</td>
<td>Neuropsychiatric inventory—nursing home version</td>
<td>No at end point</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Wimbilad et al 2001</td>
<td>10 mg</td>
<td>Sex</td>
<td>Gottfries-Brane-Steen scale—3 (0)</td>
<td>—</td>
<td>—</td>
<td>Gottfries-Brane-Steen scale</td>
<td>Yes</td>
<td>Inconsistent report‡</td>
</tr>
<tr>
<td>AD2000 Collaborative Group 2004</td>
<td>5 mg or 10 mg</td>
<td></td>
<td>Not reported adequately for the Bristol activities of daily living scale</td>
<td>5 mg and 10 mg not analysed separately</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Diverse problems, no clear duration of study, double randomisation</td>
</tr>
<tr>
<td>Holmes et al 2004</td>
<td>10 mg</td>
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ADAS-cog=Alzheimer’s disease assessment scale—cognitive subscale.
CIBIC-plus=Clinician’s interview based impression of change with caregiver input.
CGIC=Clinical global impression of change.
J-CGIC=Japanese version of the CGIC.
*Refers to the intention to treat population.
†This criterion is satisfied, when several primary end points were calculated without correction for multiplicity and the presented results after correction exceed the significance level of 5%.
‡To adjust for multiple comparisons we used the Bonferroni method. As many trials do not report the number of attempted comparisons, the minimum number of reported independent tests concerning primary end points was used for adjustment. For example, in the study by Burns et al8 two dose groups of donepezil and two primary outcome measures were specified; ADAS-cog and CIBIC-plus. Therefore four comparisons were assumed for Bonferroni adjustment, leading to a required level of 0.05/4=0.0125. This, in spite of an ambiguous definition of the evaluation procedure for the CIBIC-plus in the original publication, which allowed for much more methods of comparison, all of which are mentioned in the results section of the study: comparison of means and of fractions, applying various cut-points. Assuming four comparisons, one end point did not reach the adjusted level: the comparison of donepezil 5 mg with placebo on the CIBIC-plus scores (P>0.05): placebo 7%; 10 mg: 18%; last observation carried forward.
§Data in tables and text, statements in text and abstract or study results, and abstracts of presentations at congresses are discrepant.

Molts et al15 used as their primary end point the “median time in days to reach clinically evident functional decline,” defined as a decline of at least one point in “basic activities of daily living (ADL)” or “instrumental activities of daily living” according to the Alzheimer’s disease functional assessment and change scale or an increase in global clinical dementia rating of 1 point or more (all measures compared with baseline). The authors report that investigators were instructed to use these criteria. However, the final decision to remove a patient from the assigned treatment was left to the clinical judgment of the investigator. This is a methodological shortcoming since investigators could employ subjective measures to withdraw patients from the trial. Furthermore, 20% of placebo patients and 28% of donepezil patients discontinued the trial prematurely without reaching the predefined end point, which affects the results considerably. A further shortcoming is the restriction to report clinically evident functional decline over a period of only 48 weeks, although the study lasted for 54 weeks.

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The AD2000 Collaborative Group used as its primary end points entry to institutional care and, similarly to Mohs et al, progression of disability. One important methodological flaw is that the duration of the study was not defined in advance. In addition, the results are presented for the combined groups receiving 5 mg and 10 mg donepezil, although groups should have been tested separately. Therefore this study can neither be used as a proof of inefficacy nor as a proof of efficacy of donepezil.

Holmes et al report that patients with Alzheimer’s disease and neuropsychiatric symptoms were treated with open label donepezil for 12 weeks. During this treatment phase, patients with poor compliance, adverse events, and deterioration of neuropsychiatric symptoms or cognitive capacity were excluded. The remaining patients were randomised (double blind) between continuation of treatment and withdrawal of drug. The results show a negative effect of withdrawal of donepezil: neuropsychiatric symptoms increased when the drug was withdrawn. However, side effects of drug withdrawal are no proof for the efficacy of donepezil.
**Adverse events of cholinesterase inhibitors**

As shown in tables 3 and 4, donepezil, rivastigmine, and galantamine caused a broad spectrum of adverse events—nausea, vomiting, diarrhoea, and weight loss were the most common. The tables show the proportions of adverse events observed in patients in whom the difference between the cholinesterase inhibitor and placebo reached significance at the 5% level.

As adverse events are typical for cholinesterase inhibitors, they can affect the efficiency of blinding, because the raters might be able to guess the patient's treatment.

**Discussion**

The scientific basis for recommending donepezil, rivastigmine, or galantamine as preferred treatment for patients with Alzheimer's disease is questionable because minimal benefits were measured on rating scales and the methodological quality of the available trials was poor.

Nineteen out of 22 randomised controlled trials evaluating the efficacy of donepezil, rivastigmine, and galantamine show significant differences between treatment groups and placebo, indicating a beneficial effect of cholinesterase inhibitors, but the differences are rather moderate. The gains of 1.5-3.9 points in cognitive function, as measured with the Alzheimer’s disease assessment scale, fall below the 4 points that a panel of experts from the US Food and Drug Administration proposed as the minimum of a clinically important effect. However, the FDA's assumption that 4 points on the Alzheimer’s disease assessment scale is clinically relevant is an expert opinion and presumably not evidence based.

The results on the clinician's interview based impression of change with caregiver input scale, measuring the global function of patients, are moderate as well. The reported differences of 0.26-0.54 points are smaller than the allowed variation for one patient who can only get full scores. Also, the retest reliability of the scale is reported to range from 0.4 points to 0.6 points.

Owing to several methodological shortcomings, the validity of the reported small findings seems to be limited. Missing rigour might have led to an overestimation of beneficial effects. On the other hand, the trials provide clear evidence for considerable adverse events.

**Comparison with other studies**

The results of our review are in contrast to numerous publications that support the use of cholinesterase inhibitors. The reason for this discrepancy can be explained by differences in assessment criteria for the methodological quality of the trials. For example, the Cochrane systematic review on donepezil reports clinical efficacy of donepezil despite reporting the fact that only three of the included studies describe the method of randomisation in sufficient detail and that dropout rates were considerable. In the Cochrane review on galantamine, the randomisation procedure was the sole indicator of methodological quality of the included trials, and the higher rates of dropouts in patients treated with galantamine did not lead to a different interpretation of results. Also, dropout rates up to 35% did not influence conclusions in the systematic review on rivastigmine by Birks et al. When summing up the three Cochrane reviews on cholinesterase inhibitors, it becomes apparent that their conclusions have been drawn without a comprehensive assessment of the methodological quality of the trials. The same problems are
Table 4 Patients with adverse events in the trials on rivastigmine and galantamine (actual data because testing for significance is not appropriate for rare effects because of insufficient power)

| Study          | Dose | Cholinesterase-inhibitor | Placebo | % of patients with adverse events on cholinesterase inhibitor (placebo) colsep="|  
|----------------|------|--------------------------|---------|--------------------------------|---------|
|                |      | Diarrhoea | Nausea | Vomiting | Weight loss | Anaemia | Dizziness | Other adverse events |
| Rivastigmine colsep="|
| Agid 1998††     | 4 mg | 136         | 133     | 7 (2)*  | 17 (6)*     | 10 (3)* | —         | 6 (7) | — | colsep="|  |
| 6 mg           | 133  | 133         | 133     | 12 (2)* | 31 (6)*     | 18 (3)* | —         | 20 (7)*| — | colsep="|  |
| Cone-Bloom 1998‡‡ | 1-4 mg | 233   | 235     | —       | 8 (3)*       | 5 (2)*  | —         | 8 (4)  | Dysepsis: 6 (1)* Sinusitis: 1 (1) colsep="|  |
| 6-12 mg        | 231  | —          | 235     | —       | 20 (3)*      | 16 (2)* | —         | 14 (4)*| Dysepsis: 5 (1)* Sinusitis: 4 (1) colsep="|  |
| Fronet 1999‡    | 45   | 24         | 24      | —       | 58 (8)*      | 38 (4)* | 18 (6)*   | 27 (9)*| — | colsep="|  |
| 6-12 mg twice daily | 45   | —       | 24      | —       | 58 (8)*      | 31 (4)* | 16 (6)*   | 9 (0)  | Headache: 16 (4) colsep="|  |
| Rösler 1999‡‡   | 1-4 mg | 243   | 239     | 10 (9)  | 17 (10)*     | 8 (8)   | 3 (2)     | 10 (7) | Headache: 7 (8) colsep="|  |
| 6-12 mg        | 243  | 17 (9)*    | 50 (10)*| 34 (6)*  | 14 (2)*      | 20 (7)* | —         | —     | colsep="|  |
| Potkin 2001††   | 3-9 mg | 20    | 7       | —       | —          | —       | —         | —     | — | colsep="|  |
| Galantamine colsep="|
| Raskind 2000‡‡ | 24 mg | 212     | 213     | 12 (10) | 37 (13)*     | 21 (8)* | 12 (5)*   | 14 (11)| — | colsep="|  |
| 32 mg          | 211  | 213       | 213     | 19 (10)*| 44 (13)*     | 26 (8)* | 11 (5)*   | 19 (11)| — | colsep="|  |
| Rockwood 2001††| 24-32 mg | 261   | 125     | 32 (11)*| 15 (4)*      | 12 (2)* | 15 (4)*   | —     | Ajagination: 6 (1)* Somnolence: 8 (1)* colsep="|  |
| Tanot 2000‡‡   | 8 mg  | 140       | 286     | 5 (6)   | 6 (5)       | 4 (1)   | 6 (3)     | —     | — | colsep="|  |
| 16 mg          | 279  | 286       | 286     | 12 (6)* | 13 (5)*      | 6 (1)*  | 7 (3)     | —     | — | colsep="|  |
| 24 mg          | 273  | 286       | 286     | 6 (6)   | 17 (5)*      | 10 (1)* | 9 (3)*    | —     | — | colsep="|  |
| Wilcock 2000‡‡ | 24 mg | 220     | 215     | 7 (7)   | 37 (12)*     | 20 (4)* | 8 (1)*    | 11 (5)*| Anorexia: 10 (0)* colsep="|  |
| 32 mg          | 218  | 215       | 215     | 13 (7)* | 40 (12)*     | 17 (4)* | 5 (1)*    | 12 (5)*| Anorexia: 11 (0)* colsep="|  |
| Wilkinson 2001††| 18 mg | 88       | 87      | 2 (2)   | 17 (3)*      | 17 (5)* | —         | 5 (3)  | Headache: 6 (5) colsep="|  |
| 24 mg          | 56   | 87        | 87      | 5 (2)   | 18 (3)*      | 7 (5)   | —         | 4 (3)  | Headache: 11 (5) colsep="|  |
| 36 mg          | 94   | 94        | 94      | 4 (2)   | 37 (3)*      | 17 (5)* | —         | 7 (3)  | Headache: 15 (5) colsep="|  |

†Not reported.
‡Differences reach significance (P<0.05).
§Data shown represent the maintenance phase of the trial (week 8-26).

found in meta-analyses. Whitehead et al performed a meta-analysis of individual patients’ data from randomised controlled trials on donepezil, and Ritchie et al carried out a meta-analysis of published data from randomised controlled trials on donepezil, rivastigmine, and galantamine. No attempt was made in either meta-analysis to consider the quality of the included trials. Since all individual trials show considerable methodological shortcomings, the results of both meta-analyses are questionable as well. The same lack of assessment of methodological quality of the reviewed trials is found in the review of the American Academy of Neurology.3

Conclusions
Clinicians often argue that cholinesterase inhibitors have an effect in a subgroup of only 10-20% of patients with Alzheimer’s disease. As this subgroup cannot be identified in advance, they conclude that all patients with Alzheimer’s disease should be treated. From a scientific point of view, three replies seem justified. Firstly, this observation could also be due to a placebo effect. Secondly, if there are subgroups of patients who benefit from research should focus on the definition of responders. Thirdly, if the efficacy of the drugs is tested at the level of individual patients, clear reassessment procedures are needed for clinical practice.

Acknowledgements: We thank Michael M Kochen, Göttingen, for constant support and critical advice and Heinz-Peter Romberg, Bonn, for continuous collection of information on cholinesterase inhibitors. We also thank the members of the German Association of General Practitioners (DEGAM) for their interest and precious discussion of the subject on several occasions.

Contributors: HK, TZ and HPBB developed the design of this review, performed the literature search, analysed and interpreted the trials. The article was written by HK and revised repeatedly by TZ, HPBB, and HvdB. The final version was approved by HvdB. HK is the guarantor.

What is already known on this topic
It is generally assumed that several randomised controlled trials have proved the beneficial effect of cholinesterase inhibitors in patients with Alzheimer’s disease on cognitive and global outcome measures
Numerous “evidence based reviews” support this assumption

What this study adds
Recommendations for the use of cholinesterase inhibitors do not seem to be evidence based
Benefits measured on rating scales were minimal

The methodological quality of the available trials was poor
Funding: None.
Competing interests: None declared.
Ethics approval: Not required.

(Accepted 29 April 2005)

bmj.com 2005;331:321

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