RESEARCH PROTOCOL

The Clinical and Cost-Effectiveness of Donepezil, Rivastigmine, Galantamine, and Memantine for Alzheimer’s Disease

Southampton Health Technology Assessments Centre
Wessex Institute for Health Research and Development

March 2004
Final version.

A. Details of review team

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B. Full title of research question

- To assess the clinical effectiveness and cost effectiveness of donepezil, rivastigmine, galantamine, and memantine for Alzheimer’s Disease

C. Clarification of research question and scope

- This is an update report for donepezil, rivastigmine and galantamine (first being completed 2000) and a new report for memantine.

- The aim of the review is to a) provide a review of the clinical effectiveness and cost effectiveness of the symptomatic treatments of donepezil, rivastigmine, and galantamine for people suffering from mild to moderately-severe Alzheimer’s disease; and b) to provide a review of the clinical effectiveness and cost effectiveness of memantine for the symptomatic treatment of moderately-severe to severe Alzheimer’s disease.

- The review will include the above said drugs for the treatment of Alzheimer's disease in line with their market approval for disease severity.

- Evidence will focus on Randomised Controlled Trials comparing the interventions with placebo, non-drug comparators, or comparisons between the interventions.
• The review will be from an NHS and personal social services perspective (costs and benefits). Baseline analysis will be limited to an NHS and PSS perspective, but where the evidence suggests there might be important costs falling on carers or other non-NHS organisations, or carer benefits, these will be noted separately, and where possible separate analysis will be reported.

D. Report methods

• The review will be undertaken as systematically as time allows following the general principles outlined in NHS CRD Report 4.

• The research protocol will be updated as necessary as the research programme progresses. Any changes in the protocol will be notified to NCCHTA and NICE.

Search strategy

• Electronic databases that will be searched include: Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, NHS CRD (University of York) DARE and NHS EED, Medline (Ovid), PubMed, Embase, National Research Register, Current Controlled Trials, PsycInfo, Science Citation Index, Web of Science Proceedings, BIOSIS, HTA, Clinical trials.gov

• Searches for donepezil, rivastigmine and galantamine will be for the period from 2000 to 2004 and will be limited to English language. Searches for memantine will be for the period from the inception of the database until July 2004 and will be limited to English language.

• Bibliographies of related papers will be assessed for relevant studies.

• Experts will be contacted for advice and peer review, and to identify additional published and unpublished references.

• Manufacturer and sponsor submissions to the National Institute for Clinical Excellence (NICE) will be searched for studies that meet the inclusion criteria.

Inclusion and exclusion criteria

• Interventions include the four drugs donepezil, rivastigmine, galantamine and memantine for Alzheimer’s disease.

• Participants include those people diagnosed with probable Alzheimer’s disease (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) and/or DSM-III/IV criteria) that meet the criteria for treatment with donepezil, rivastigmine, galantamine, (mild to moderately-severe Alzheimer’s disease, usually associated with a MMSE score of 10-26) and memantine (moderately-severe to severe Alzheimer’s disease)

  o Although the interventions included are licensed for specific conditions, it is evident that studies use different terms to describe the same condition. For example, patients with mild to moderately-severe Alzheimer’s disease according to recognised criteria may be described as having mild to moderate Alzheimer’s disease or having a

1 Searches prior to 2000 were undertaken in the previous technology assessment report and will also be used to source eligible trials for this update review.
MMSE of 10-26 in a trial report. Also patients with moderately-severe to severe Alzheimer’s disease may be described as moderate to severe. The review will include trials using any of these terms to describe the patients condition, assessing any apparent differences through sensitivity analysis.

- If the MMSE cited in each trial falls outside of the range suggested above, or reports another measure of severity, a pragmatic decision will be taken to use the definition reported in individual trials, and to note any differences in the review.

- Trials of participants with mixed dementia types will be included when the predominant dementia is Alzheimer's disease. Trials will not be included if the predominant dementia is not Alzheimer's disease, or the predominant dementia is not specified.

- Systematic reviews of randomised controlled trials (RCTs) and RCTs comparing the different drugs with placebo or each other or non-drug comparators will be included in the review of effectiveness. Systematic reviews will be used as a source for RCTs and as a comparator. Any studies published as abstracts or conference presentations will be assessed for inclusion if sufficient details are presented to make appropriate decisions about the methodology of the study and the results.

- If searches show that there is no evidence of the long term effects of treatments in terms of adverse events, then controlled clinical trials meeting the other inclusion criteria and having a duration of follow-up of 12 months or more may be considered for inclusion.

- For the review of memantine (for moderately-severe to severe Alzheimer’s disease) trials that combine memantine with either donepezil, galantamine, or rivastigmine will be included. Trials that provide memantine following on from treatment with either donepezil, galantamine, or rivastigmine will also be included.

- Outcomes will focus on those that are clinically relevant to patients with Alzheimer’s dementia and their carers. Primary outcome measures will include survival and measures of global functioning, cognition, function, behaviour and mood, health related quality of life. In addition, the systematic review will report information on secondary outcomes on adverse events, ability to remain independent, likelihood of admission to residential/nursing care, carer health related quality of life, and compliance (adherence) where they are reported in the included studies. Inclusion decisions will be made on primary outcome measures.

- Economic evaluations of donepezil, rivastigmine, galantamine and memantine in people with Alzheimer’s disease that include a comparator (or placebo) and both the costs and consequences (outcomes) of treatment will be included. Systematic reviews of economic evaluations will also be included.

- Inclusion criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Data extraction strategy

- Data will be extracted from the included studies using standard tables for the clinical and cost effectiveness studies (see Appendix 1).

- Data extraction will be undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.
Quality assessment strategy

- The quality of included systematic reviews will be assessed using NHS CRD (University of York) criteria. Quality assessment of RCTs will be judged in accordance with chapter II.5 of CRD Report 4 (2nd Edition) (see Appendix 2).

- Economic evaluations will be assessed using criteria recommended by Drummond and Jefferson (1996), and/or the format recommended and applied in the CRD NHS Economic Evaluation Database (CRD Report 6).

- Quality criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Methods of analysis/synthesis

- Clinical effectiveness will be synthesised through a narrative review with tabulation of results of included studies.

- Where evidence is available, the review will undertake subgroup analyses by disease severity.

- Data will be combined statistically if of sufficient quantity, quality and if sufficiently similar by meta-analysis using Review Manager software.

Methods for estimating quality of life, costs and cost-effectiveness and/or cost/QALY

- Published cost-effectiveness studies will be reviewed in detail, comprising a narrative review with a tabulation of results where appropriate. Cost-effectiveness studies will be identified as part of the search strategy documented above.

- Where appropriate an economic model will be devised by adapting an existing cost-effectiveness model or constructing a new one using the best available evidence to determine cost-effectiveness in a UK setting; extrapolating from shorter-term clinical data (e.g. 6-month trial data) to longer term final outcomes (i.e. modelling disease progression over time). An exploratory review of the literature indicates that product specific modelling methods have been reported to date (see background section).

- Data on resource use and costs will be from the published literature, NHS sources and industry submissions where appropriate and available. The perspective of the economic analysis will be that of the NHS and Personal Social Services. As stated above, baseline analysis will be in accordance with the perspective of the NHS and PSS, and where costs and resource use related to treatment fall outside of this perspective we will report these separately where data are available.

- Effectiveness data, in terms of the outcomes described in the above section, will be extracted from published trials and used in association with cost data to populate the model to obtain measures of cost-effectiveness. If available, quality of life information will be obtained from the literature or other sources to calculate cost utility estimates in terms of cost per quality adjusted life year (QALY). From an exploratory review of the cost-effectiveness literature we have noted the use of a variety of economic endpoints, usually using the MMSE as an indicator of disease progression (see background section).
The robustness of the results to the assumptions made in the model will be examined through sensitivity analysis and/or probabilistic sensitivity analysis.

Other considerations

- It is evident that clinical trials of treatments for dementia may be affected by changes in the clinical management of patients, particularly where it focuses on the longer term. As a consequence, the systematic review will indicate any major alterations in treatment (including stopping treatment, or cross-over between groups) stated by the studies and report whether outcomes are reported on an intention to treat.

E. Handling the company submission(s)

- Industry submissions will be checked for additional studies that meet the SHTAC inclusion criteria, for data on costs and for data on the current use of donepezil, rivastigmine, galantamine and memantine.

- Results of cost-effectiveness analyses from industry will be compared with the SHTAC analysis, but this will not be a line by line critique of sponsor models.

- Any ‘commercial in confidence’ data taken from the industry submissions will be clearly marked (underlined) in the report submitted to the HTA programme and to NICE. In addition, any information provided by others that is deemed in confidence will be marked as academic in confidence. A separate version with any such data removed will also be submitted.

Project management

It is planned to send:

- a final protocol to NCCHTA on: 11th March 2004
- an interim progress report on: 17th June 2004
- a complete and near final draft to external reviewers and NCCHTA on: 14th July 2004
- the final assessment report to NCCHTA on: 30th August 2004

b. Competing interests

none known

c. External review:

The Technology Assessment Report will be subject to external review by at least two experts acting on behalf of the NHS HTA Programme. These referees will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that the NICE secretariat and Appraisal Committee will undertake methodological review. In addition, an external methodological referee will be asked to review the report on behalf of the HTA Programme. Referees will review a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. Referees will be required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking which we will hold on file. Comments from referees and the Technical lead, together with our responses will be made available to NCCHTA in strict confidence for editorial review and approval.
Appendix 1: Data extraction forms

a. Data extraction form for RCT's

<table>
<thead>
<tr>
<th>Reviewers:</th>
<th>Reference and Design</th>
<th>Intervention and Treatment arms: (including dosage, length of treatment)</th>
<th>Participants</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>RefID:</td>
<td>Treatment arms:</td>
<td>Number of Participants:</td>
<td>Primary outcomes: (e.g ADAS-cog, MMSE, clinical dementia ratings, CIBIC-plus, Global Deterioration Scale and Progressive Deterioration Scale)</td>
<td></td>
</tr>
<tr>
<td>Author:</td>
<td></td>
<td>Sample attrition/dropout:</td>
<td>Sample crossovers:</td>
<td></td>
</tr>
<tr>
<td>Year:</td>
<td></td>
<td></td>
<td>Secondary outcomes:</td>
<td></td>
</tr>
<tr>
<td>Country:</td>
<td>Study design:</td>
<td></td>
<td>Methods of assessing outcomes:</td>
<td></td>
</tr>
<tr>
<td>Number of centres:</td>
<td></td>
<td></td>
<td>Length of follow-up:</td>
<td></td>
</tr>
<tr>
<td>Funding:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Treatment X (n= )</th>
<th>Comparator X (n= )</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QoL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments

Others

Adverse Effects

Resource Use

Methodological comments
- Allocation to treatment groups:
- Blinding:
- Comparability of treatment groups:
- Method of data analysis:
- Sample size/power calculation:
- Attrition/drop-out:

General comments
- Generalisability:
- Outcome measures:
- Inter-centre variability:
- Conflict of interests:

Comments: Please provide a summary measure or confidence interval if the study's summary measure or confidence interval is calculated. Please indicate if a summary measure or confidence interval is calculated.

Comments: Please provide the total number of participants in the study and the number of participants by intervention group.

Comments: Please state the criteria used for inclusion in the study - if none please state. This will probably include age, diagnosis, severity etc.

Comments: Please provide the total number of patients and the number per intervention group that were lost to follow-up during the study.

Comments: Please specify the total number of patients and the number per intervention group that crossed over during the study.

Comments: Please state the primary outcomes used in the study, briefly what they measure, and the time points at which these are assessed. Any details of scale interpretation should be described in comments box below each measure in the results section.

Comments: Please describe the treatment(s) and comparator(s), e.g. 1) drug A, 10mg/day, 6 weeks 2) placebo etc.

Comments: Please specify the total number of patients and the number per intervention group that were lost to follow-up during the study.

Comments: Please specify the total number of patients and the number per intervention group that crossed over during the study.

Comments: Please state the criteria used for inclusion in the study - if none please state. This will probably include age, diagnosis, severity etc.

Comments: Please provide the baseline clinical, socioeconomic & demographic characteristics etc.

Comments: Please identify the method used for assessing outcome measures.

Comments: Please identify interventions other than those under direct comparison.

Comments: Please specify the length of follow-up - stating if this differs from the randomisation schedule.

Comments: Please discuss the methods of blinding to treatment groups.

Comments: General comments on the study's generalisability, outcome measures, inter-centre variability, and conflict of interests.

Comments: Please provide the total number of participants in the study and the number of participants by intervention group.

Comments: Please state the primary outcomes used in the study, briefly what they measure, and the time points at which these are assessed. Any details of scale interpretation should be described in comments box below each measure in the results section.

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Comments: Please identify the method used for assessing outcome measures.

Comments: Please identify interventions other than those under direct comparison.

Comments: Please specify the length of follow-up - stating if this differs from the randomisation schedule.

Comments: Please discuss the methods of blinding to treatment groups.

Comments: General comments on the study's generalisability, outcome measures, inter-centre variability, and conflict of interests.
<table>
<thead>
<tr>
<th>Reference and Design</th>
<th>Methods</th>
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</thead>
<tbody>
<tr>
<td>Author</td>
<td>Aim (Question):</td>
</tr>
<tr>
<td>Year</td>
<td>Search strategy: databases searched</td>
</tr>
<tr>
<td>Ref ID</td>
<td>Inclusion criteria used</td>
</tr>
<tr>
<td>Study design:</td>
<td>Interventions:</td>
</tr>
<tr>
<td></td>
<td>Participants:</td>
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<tr>
<td></td>
<td>Outcome measures:</td>
</tr>
<tr>
<td>Study design:</td>
<td>Study design:</td>
</tr>
<tr>
<td>Quality assessment:</td>
<td></td>
</tr>
<tr>
<td>Application of methods:</td>
<td></td>
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</tbody>
</table>

Results (including):
- Quantity and quality of included studies.
- What was the combined treatment effect? (Should include point estimates and confidence intervals/standard deviations, P values etc for each outcome assessed):
- Assessment of heterogeneity:

Comments:
- e.g funding, any other methodological elements that may affect the rigour of the systematic review
### Appendix 2: Quality assessment forms

a. Quality assessment for RCTs (Quality Criteria - CRD Report 4)

**Quality criteria for assessment of experimental studies**

<table>
<thead>
<tr>
<th>Number</th>
<th>Question</th>
<th>Answer</th>
<th>Methodological Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Was the assignment to the treatment groups really random?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Was the treatment allocation concealed?</td>
<td></td>
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<tr>
<td>3</td>
<td>Were the groups similar at baseline in terms of prognostic factors?</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>Were the eligibility criteria specified?</td>
<td></td>
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<tr>
<td>5</td>
<td>Were outcome assessors blinded to the treatment allocation?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Was the care provider blinded?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Was the patient blinded?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Were the point estimates and measure of variability presented for the primary outcome measure?</td>
<td></td>
<td></td>
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<tr>
<td>9</td>
<td>Did the analyses include an intention to treat analysis?</td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td>Were withdrawals and dropouts completely described?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

b. Quality assessment for Systematic Reviews

**Quality assessment for reviews using the DARE criteria**

<table>
<thead>
<tr>
<th>Quality Item</th>
<th>Yes/No/Uncertain</th>
<th>Methodological Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Is there evidence of a substantial effort to search for all relevant research?</td>
<td></td>
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</tr>
<tr>
<td>3. Is the validity of included studies adequately assessed?</td>
<td></td>
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</tr>
<tr>
<td>4. Is sufficient detail of the individual studies presented?</td>
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<td></td>
</tr>
<tr>
<td>5. Are the primary studies summarised appropriately?</td>
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</tbody>
</table>
Appendix 3. Background

Description of underlying problem:
Dementia is a chronic progressive organic mental disorder in which there is disturbance of multiple higher cortical functions including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement.

Dementia in Alzheimer's disease is a primary degenerative cerebral disease of unknown aetiology with characteristic neuropathological and neurochemical features. The disorder is usually insidious in onset and develops slowly but steadily over a period of several years.

Progression of Alzheimer’s disease is characterised by a worsening in the domains of cognition, functional ability (e.g. activities of daily living), and behaviour and mood. Changes in one or more of these domains and their affect upon the patient and their carers’ wellbeing provide the basis for diagnosis, assessing severity and progression of the syndrome.

Diagnosis
Alzheimer’s disease (AD) is the most common cause of dementia and is characterised by an insidious onset and slow deterioration, which makes diagnosis difficult. In the majority of cases the diagnosis is one of exclusion; AD is diagnosed once other causes of dementia have been excluded.

Alzheimer’s disease is diagnosed on the basis of review of full medical history corroborated by a close relative or carer, physical examination, routine blood investigations, and mental health examination including cognitive assessment.

There are a number of different methods of assessing the severity of Alzheimer’s disease, including: Clinician's Interview-based Impression of Change (CIBIC), ADAS-cog (Alzheimer's disease assessment scale - cognitive subscale) or Mini Mental State Examination (MMSE). The 30 point MMSE (Mini Mental State Examination) is commonly used. Mild AD is usually associated with an MMSE of 21 to 26, moderate AD is usually associated with an MMSE of 10 to 20 and severe AD is usually associated with an MMSE of less than 10.

Epidemiology
Approximately 750,000 people in the UK have dementia (Alzheimer society). This represents 5% of the total population aged 65 and over, and 20% of the population aged 80 and over. Alzheimer's disease is the most common form of dementia accounting for approximately 55% of people with dementia. The prevalence of dementia increases with age rising from under 1% in 60 years old to over 30% in 90% year olds.

There are few data on prevalence by severity. Two community based surveys report Mini Mental State Score (MMSE). Some 50-64% of those with AD were classified as mild to moderate severity (Jagger 1995; Walsh 1990). In another sample this was in the region of 74% (Evans 1991)

Current Services
For people with suspected dementia, early diagnosis allows access to treatment, planning for the future and the opportunity to try and come to terms with their condition. It provides the person and their carers with the opportunity to understand any changes in memory, behaviour or personality which can have a devastating effect on their lives. Initial diagnosis involves taking a history with carer involvement, using assessment scales to aid diagnosis and establish severity, as well as carrying out physical examinations and investigations. The initial diagnostic process is usually undertaken by their GP, who will then refer on to specialist services such as a memory clinic, psychiatrist and/or Community Mental Health Team for Older People. The memory clinic/psychiatrist will assess the patient to confirm any diagnosis, which may involve the use of CT scans.
Treatment of dementia involves several steps. It is important to explain the diagnosis to the patient and the carer, providing relevant information about help and support. Also the patient and carer should be informed of the likely prognosis and options for packages of care. It may be appropriate to make referrals to help with fears and worries, distress, practical and financial issues that may affect the person and carer. It will be important to provide reassurance to the patient of the unique qualities of people with dementia, whilst recognising their personal and social needs. Options for treatment include non-pharmacological management strategies such as mental exercise, physical therapy and dietary treatment with drug therapy, which are aimed at slowing the progression of the condition. It may be necessary to prescribe antipsychotic drugs for delusions and hallucinations, distress or extreme behaviour disturbance. For those patients with mild to moderately-severe Alzheimer’s dementia, NICE has recommended use of donepezil, rivastigmine and galantamine under specific conditions. Treatment decisions will usually be made by the psychiatrist in consultation with the patient and their carers.

It is important to involve the specialist mental health services when the diagnosis is uncertain, when specific behavioural and psychological symptoms are present or there are safety concerns about the patient. Also, it may be helpful when assessing the ability of patients to continue to undertake activities such as driving or risk assessment for abuse or self harm. Patients with multiple or complex problems, or with a dual diagnosis or who are being considered for antidementia drug treatment should also be referred to specialist services. Carers should get access to specialist services too, providing counselling and respite care. The Community Mental Health Team for Older People will assess the patients’ needs for social services, support, day care sitting service and benefits. In addition, they will consider the needs of the carer in terms of information about the condition, support and respite care.

The interventions under review
Alzheimer’s disease is associated with the loss of cholinergic neurones and falling levels of the neurotransmitter acetylcholine. Donepezil, galantamine and rivastigmine are cholinesterase inhibitors, and raise the concentration of acetylcholine at sites of neurotransmission. Galantamine also enhances the action of acetylcholine on nicotinic receptors, and rivastigmine is also a butyrolcholinesterase inhibitor which further enhances cholinergic activity.

Memantine is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate.

Donepezil, rivastigmine & galantamine have marketing authorisation for use in mild to moderately severe Alzheimer's disease, and memantine has marketing authorisation for use in moderately severe to severe Alzheimer's disease.

Costs
Dementia exacts a large social and economic toll on patients, their families and carers, and the health and social services. Direct cost of Alzheimer’s disease was over £1 billion in 1993 in England. When added to the costs of informal caring and to other statutory agencies, the total cost is thought to be around £6 billion.

Cost-effectiveness
Indications from the present literature are that the cost-effectiveness of technologies has been estimated using a range of methodological approaches and economic endpoints. For example, economic models have been developed to estimate the cost-effectiveness of donepezil, rivastigmine and galantamine (literature on memantine not yet considered), and for each of the products it appears that a different approach has been taken to the estimation of outcomes within the cost-effectiveness analysis.

In published cost-effectiveness models, outcome estimates for donepezil are calculated based on a range of methods to model disease progression, but all would appear to use transition probabilities
(from trial data and/or observational datasets) to predict when and if patients progress from disease states defined using MMSE scores. In the economic evaluations published for rivastigmine survival analysis/hazard models have been used to estimate the likelihood that a patient will remain in his or her current MMSE defined health state at any given point in time (or whether they will transit to another health state). Whilst for galantamine, the published economic evaluations use predictive equations (risk equations) derived from statistical analysis of data from a longitudinal observational study on patients with AD.

Economic endpoints in the published cost-effectiveness studies also vary by/within product. For example the economic evaluation of donepezil estimates difference (treatment group versus placebo) in time spent in a non-severe AD health state (MMSE >10), whilst the cost-effectiveness of rivastigmine is characterised using delay in cognitive decline as an outcome, and economic outcomes in the published galantamine studies are based on delay in the progression of disease to the point where patients need full time care (FTC).

The MMSE has been commonly used in economic studies to characterise disease progression and/or cognitive decline, with variation in studies on the number of health states used to define the progression of disease. The validity of the MMSE as a meaningful outcome measure in economic studies has been questioned on a number of grounds, including the use of trials of a short duration (e.g. often 6 months or less) and the difficulty in making meaningful observations for a disease that is slow to progress over a number of years (Shukla et al, 2000).

References


7. MF Drummond, TO Jefferson. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ*. 1996;313:275-283


Provide the baseline clinical, socioeconomic & demographic characteristics presented for the different intervention groups - stating any notable differences between the groups.

Identify the method used for assessing outcomes - specifically if any background was provided on who undertook assessments etc. Details provided should be brief with any methodological issues discussed in the methodological comments section of the data extraction (e.g. whether appropriate arrangements for blinding assessment were in place; training assessors etc...any bias?)

Identify interventions other than those under direct comparison that are given to patients, which may have some effect on the outcomes of treatment

Specify the length of follow-up - stating if this differs from any period stated a priori. If there are any differences between groups or any other important variations please state.

The results section provides a basic structure that will require adaptation for the different studies included in the review. Actual point estimates and confidence intervals/standard deviation etc should be put in the columns provided and any important comments added to the comments section. Data should include the numerator and denominator as well as the point estimate.

The method of allocation should be discussed and any possible biases briefly discussed. If there are no comparators this should be stated.

This section should discuss the methods of blinding to treatment and to assessment among patients and assessors.

Comments should be made about any differences in baseline characteristics of patients in the different intervention groups, so judgements can be made about the effects on outcomes.

Was the method of statistical analysis appropriate for the study? (for the outcomes we are including only) Were outcomes reported on an intention to treat basis? Were point estimates and confidence intervals stated?

Did the study calculate a priori sample sizes? Were power calculations undertaken? Were the outcomes for which sample sizes/power were calculated those that were discussed and/or significant?

Did the study present information on attrition/drop-outs? Would the attrition reported have had any effect on outcomes?

The section on general comments should present information about the study that may be relevant to the evidence presented not already discussed. Some categories are
suggested but these do not have to be completed for all studies and may be deleted. Additional areas of concern may be included.

<table>
<thead>
<tr>
<th>Page 7: [13] Comment</th>
<th>NCCHTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the inclusion/exclusion criteria limit the applicability of the study to a specific population group or setting?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Page 7: [14] Comment</th>
<th>NCCHTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the outcome measures relevant to the study area? Were they measured appropriately?</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Page 7: [15] Comment</th>
<th>NCCHTA</th>
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</thead>
<tbody>
<tr>
<td>If there was more than one centre included in the study, were there variations between them? What effect would it have on outcomes?</td>
<td></td>
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<thead>
<tr>
<th>Page 7: [16] Comment</th>
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<tr>
<td>Who funded the research? State specific organisation</td>
<td></td>
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</tbody>
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