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Rapid review

Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review

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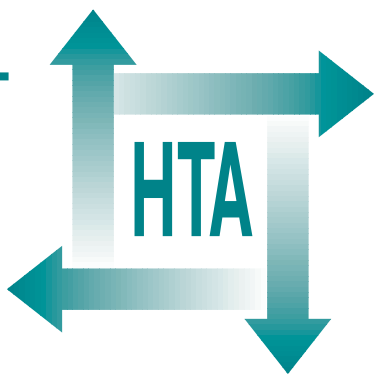
NHS R&D HTA Programme



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Contents

Glossary and list of abbreviations

AChEIs	acetylcholinesterase inhibitors
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale cognitive subscale. Maximum impairment is 70; lower scores indicate less severity
ADCS	Alzheimer's Disease Cooperative Study*
ADL	Uniform Activities of Daily Living
BDS	Blessed Dementia Scale*
BNF	*British National Formulary*
BVR	Benton Visual Retention*
CDR-SB	Clinical Dementia Rating Scale – Sum of the Boxes
CEA	cost-effectiveness analysis*
CGIC	Clinical Global Impression of Change
CIBIC	Clinician's Interview-based Impression of Change
CIC	commercial in confidence
CPMP	Committee on Proprietary Medicinal Products
CRD	NHS Centre for Reviews and Dissemination
CT	computed tomography
CUA	cost–utility analysis*
DAD	Disability Assessment for Dementia scale*
DEC	Development and Evaluation Committee
DSM-4	Diagnostic and Statistical Manual of mental disorders
EQ-5D	EuroQoL
FDA	Food and Drug Administration
FOME	Fuld Object Memory Evaluation*
GBS	Gottries–Brane–Steen scale*
GDS	Global Deterioration Scale*
HTA	Health Technology Assessment
HUI	Health Utilities Index (versions II or III)*
IADL	Instrumental Activities of Daily Living*
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
IDDD	Interview for Deterioration in Daily living in Dementia*
IHQL	Index of Health Related Quality of Life*
ITT	intention-to-treat analysis
LOCF	last observation carried forward
MMSE	Mini-mental State Examination
MRI	magnetic resonance imaging
N/A	not assessed*
NICE	National Institute for Clinical Excellence
NINCDS-ADRDA	National Institute of Neurology and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
NNT	number-needed-to-treat
NOSGP	Nurse Observation Scale for Geriatric Patients*

continued

continued

NPI	Neuropsychiatric Inventory
ns	not statistically significant*
OC	observed case
PDS	Progressive Deterioration Scale
PCG	Primary Care Group
PCT	Primary Care Trust
PSMS	Physical Self-Maintenance Scale*
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RDO	retrieved drop-out*
SEM	standard error of mean
TESS	treatment-emergent signs and symptoms*
URI	upper respiratory tract infection*
UTI	urinary tract infection*
WMD	weighted mean difference*

* Used only in tables

Executive summary

Background

Alzheimer's disease is the most common cause of dementia and is characterised by an insidious onset and slow deterioration. The estimated prevalence of Alzheimer's disease for a standard health authority (500,000 people) is about 3330. Current service involves a wide range of agencies, and drug therapy for some patients.

Objectives

To provide a rapid and systematic review of the clinical effectiveness and cost-effectiveness of donepezil, rivastigmine and galantamine in the symptomatic treatment of people suffering from Alzheimer's disease.

Methods

A systematic review of the literature was undertaken.

Data sources

Searches were made of electronic databases, including MEDLINE, EMBASE, The Cochrane Library, Database of Abstracts of Reviews of Effectiveness, NHS Economic Evaluation Database, National Research Register, Science Citation Index, BIOSIS, EconLit, MRC Trials database, Early Warning System, Current Controlled Trials, TOXLINE, Index of Scientific and Technical Proceedings, and Getting Easier Access to Reviews. All sources were searched over the period covered by the databases up to March/July 2000. Bibliographies of related papers were assessed for relevant studies and experts were contacted for advice and peer review, and to identify additional published and unpublished references. Manufacturer submissions to the National Institute for Clinical Excellence (NICE) were reviewed.

Study selection

Studies were included if they fulfilled the following criteria.

- Intervention: donepezil, rivastigmine or galantamine used to treat Alzheimer's disease.
- Participants: people diagnosed with Alzheimer's disease who meet the criteria for treatment with donepezil, rivastigmine and galantamine.
- Outcomes: measures assessing changes in cognition, function, behaviour and mood, quality of life (including studies assessing carer well-being and carer-input), and time to institutionalisation.
- Design: systematic reviews of randomised controlled trials (RCTs) and RCTs comparing donepezil, rivastigmine or galantamine with placebo or each other or non-drug comparators were included in the review of effectiveness. Economic studies of donepezil, rivastigmine or galantamine used to treat Alzheimer's disease that included a comparator (or placebo) and both the costs and consequence (outcomes) of treatment were included in the review of cost-effectiveness.

Studies in non-English language, and abstracts and conference poster presentations of systematic reviews, RCTs and economic evaluations were excluded.

Two reviewers identified studies by independently screening study titles and abstracts, and then by examining the full text of selected studies to decide inclusion.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion. The quality of RCTs was assessed using the Jadad scale and the quality of systematic reviews was assessed using criteria developed by the NHS Centre for Reviews and Dissemination. The quality of economic evaluation studies was assessed by their internal validity (i.e. the methods used) using a standard checklist, and external validity (i.e. the generalisability of the economic study to the population of interest) using a series of relevant questions.

Data synthesis

The clinical effectiveness and cost-effectiveness of donepezil, rivastigmine and galantamine were synthesised through a narrative review with full tabulation of results of all included studies. In the

economic evaluation, the reviewers assessed whether adjustments could be made to existing models to reflect the current situation in England and Wales.

Results

Clinical effectiveness

- Donepezil – three systematic reviews and five RCTs (plus four studies from industry*) were found. Results suggest that donepezil is beneficial when assessed using global and cognitive outcome measures.
- Rivastigmine – three systematic reviews and five RCTs (plus two studies from industry*) were found. Results suggest that rivastigmine is beneficial in terms of global outcome measures.
- Galantamine – one systematic review and three RCTs (plus three studies from industry*) were found. Results suggest that galantamine is beneficial in terms of global, cognitive and functional scales.

Summary of benefits

It is difficult to quantify benefits from the evidence available in the literature. Statistically significant improvements in tests such as ADAS-cog (Alzheimer's Disease Assessment Scale cognitive subscale) may not be reflected in changes in daily life.

Costs/cost-effectiveness

Nine economic studies were found, which could not be closely compared.

- Donepezil – the five studies of donepezil produced a variety of cost-effectiveness estimates. While the base cases showed increased effectiveness and were cost saving in two studies, they were more costly in the other three. When sensitivity analyses are taken into consideration, estimates fluctuated more widely and there were, in some cases, conflicting results for sub-group analyses, thus casting doubt on the robustness of the estimates.
- Rivastigmine – of the four rivastigmine studies, the oldest has been surpassed by more recent evaluations. Cost-effectiveness ratios in two studies could not be extracted as the associated overall effectiveness was not reported and interpretation of the costs results alone is difficult due to the exclusion of drug therapy costs. The fourth study found average net costs within the first year, but a cost saving at 2 years, but it was not clear whether the data presented could be translated into incremental cost-effectiveness ratios.
- Galantamine – no published economic evaluations of galantamine were found.

For each drug there was a further economic analysis performed by industry*.

Economic implications of prescribing these drugs are uncertain. The main issue is not drug costs *per se*, but the impact across different sectors. Currently, this remains unclear since the financing and provision of care for patients with Alzheimer's disease in England and Wales is complex and difficult to unravel. Any cost savings would depend mainly on release of funds from residential care.

Conclusions

Implications

On the basis of the current evidence, the implications of the use of donepezil, rivastigmine or galantamine to treat patients with Alzheimer's disease are unclear. The main issue is whether the modest benefits seen in the outcome measures used in the trials would translate into benefits significant to patients.

Future research

Future research should include: development of quality-of-life instruments for patients and their carers; comparisons of benefits from drugs with those from other interventions; identification of those patients likely to benefit from drug treatment; development of protocols of treatment withdrawal if not beneficial; economic evaluations. Ongoing research should provide valuable evidence.

* Unpublished data, submitted as commercial in confidence

Chapter 1
Introduction

Aim of the review

The aim of the review is to provide a rapid and systematic review of the clinical effectiveness and cost-effectiveness of donepezil, rivastigmine and galantamine in the symptomatic treatment of people suffering from Alzheimer's disease (AD).

Background

Description of underlying health 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. AD is the commonest cause of dementia and is characterised by an insidious onset and slow deterioration, which makes diagnosis difficult. In the majority of cases diagnosis is made on clinical grounds alone, after other causes of dementia have been excluded clinically and by laboratory investigation.

Several different diagnostic criteria for AD have been developed. The most generally accepted clinical diagnostic criteria are those of the NINCDS-ADRDA[*1] (McKhann Criteria), which provide clinical guidance for 'possible', 'probable' and 'definite' diagnosis of AD. The sensitivity and specificity of the criteria have been estimated as 0.81 to 0.92 and 0.13 to 0.80, respectively, compared with pathological diagnosis.[2] However, in the UK, clinicians tend to use the DSM-4[†] and ICD-10[‡] criteria.

Definitive diagnosis of AD requires demonstration of pathological features in brain tissue such as degeneration of specific nerve cells and the presence of neuritic plaques and neurofibrillary tangles. The main differential diagnosis is with multi-infarct dementia and Lewy body dementia.

Incidence and prevalence

The Alzheimer's Society estimates that there are approximately 750,000 people with dementia living in the UK, of whom about 413,000 have AD.[3]

There are few data on prevalence by severity. Two community-based surveys report Mini-Mental State Score (MMSE), which has been used to define severity in some clinical trials.[4,5] These surveys found that 50–64% of people in the community with AD had scores between 13 and 24 (mild/moderate severity). Although this range is narrower than that used as an inclusion criterion in some clinical trials, it provides an estimate of the likely proportion of patients that might be considered for treatment on the basis of severity alone. Evans and colleagues,[6] using non-specified cognitive measures, classified 74% of people diagnosed with AD in a community (non-institutionalised) sample as mild to moderately impaired. Incidence of AD appears to have been stable over the past two decades,[4] although demographic changes will result in an increase in prevalence.

Table 1 shows the prevalence of AD (all grades of severity) in England and Wales based on data from Morbidity Statistics from General Practice 1991–1992.[7]

Tables 2 and *3* use the prevalence rates for all dementia from the EURODEM study to provide an estimate of the prevalence of AD for the population of a standard health authority and a primary care group/primary care trust (PCG/PCT). Assuming that AD accounts for 55% of dementia[3] and that 60% of Alzheimer's patients have the mild to moderate form of the disease,[8] a health authority might expect approximately 3327 cases of AD, of which 2000 would be the mild to moderate form of the disease. In a PCG or PCT with a population of 200,000 people, there are likely to be around 1330 cases of AD, with 798 people having mild to moderate disease.

[*] National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association

[†] Diagnostic and Statistical Manual for mental disorders

[‡] International Classification of Diseases version 10

TABLE 1 *Prevalence of AD (ICD 331.0) by sex and age, 1991–1992*[7]

Age (years)	Cases		Patient years at risk		Rate/10,000 patient years at risk	
	Men	Women	Men	Women	Men	Women
45–64	3	2	50,013.3	49,102.6	0.6	0.4
65–74	6	9	17,144.5	21,090.4	3.5	4.3
75–84	12	16	8,733.4	14,618.0	13.7	10.9
≥ 85	3	7	1,682.8	5,074.7	17.8	13.8
All ages	24	34	229,221.9	238,810.6	1.0	1.4

TABLE 2 *Estimated prevalence of AD (ICD 331.0) by age for a standard health authority*[3,8,9]

Age group (years)	Standard health authority (population 500,000 people)					
	Population	Prevalence of dementia (rate/100 people)		Estimated prevalence of dementia	Estimated prevalence of AD	Estimated prevalence of mild to moderate AD
		Men	Women			
45–64	114,527	0.06	0.06	69	38	23
65–69	22,326	2.20	1.10	362	199	119
70–74	20,190	4.60	3.90	851	468	281
75–79	16,301	5.00	6.70	980	539	323
80–84	10,932	12.10	13.50	1422	782	469
≥ 85	9,470	21.50	26.20	2365	1301	780
Total ≥ 45	–	–	–	6048	3327	1996

TABLE 3 *Estimated prevalence of AD (ICD 331.0) by age for a PCG/PCT*[3,8,9]

Age group (years)	Standard PCG/PCT (population 200,000 people)					
	Population	Prevalence of dementia (rate/100 people)		Estimated prevalence of dementia	Estimated prevalence of AD	Estimated prevalence of mild to moderate AD
		Men	Women			
45–64	45,811	0.06	0.06	27	15	9
65–69	8,930	2.20	1.10	145	80	48
70–74	8,076	4.60	3.90	340	187	112
75–79	6,520	5.00	6.70	392	216	129
80–84	4,373	12.10	13.50	569	313	188
≥ 85	3,788	21.50	26.20	946	520	312
Total ≥ 45	–	–	–	2419	1330	798

Current service

The clinical management of AD is centred on as early and accurate a diagnosis as possible and provision of appropriate services to patients and carers.

Diagnosis must eliminate disorders and dementia other than AD. Diagnosis normally takes place in the primary care setting. Most people with early dementia are not investigated by specialist services, but are referred later at more advanced

stages when they or their carer(s) have greater need for support (either in the community or from inpatient or day-care services), or in reaction to a crisis. This is partly because clinical diagnosis has been considered sufficiently accurate,[10] or because few cases of dementia are due to remediable causes.[11] The use of routine computed tomography (CT) scanning has been advocated, but is only worthwhile in selected cases.[12] The elements of diagnosis include: a full medical history corroborated by a close relative or carer; mental health examination including cognitive assessment; physical examination; routine blood investigations; special investigations such as magnetic resonance imaging (MRI) and CT scans used selectively when indicated.

Management of AD involves treatment of cognitive symptoms, and treatment of non-cognitive symptoms such as agitation and hallucinations. Management includes day care, respite admissions, and night care, to ease the burden on carers. Acetylcholinesterase-inhibiting drugs have been suggested for the treatment of cognitive symptoms of AD, specifically for mild to moderate disease. These include donepezil and rivastigmine. Another drug, tacrine, has been available in the USA and France for several years but has not yet received marketing authorisation in the UK. It will probably not be licensed in the UK because of side-effects, particularly liver toxicity.

The Standing Medical Advisory Committee issued guidance in April 1998 that donepezil treatment should be initiated and supervised only by a specialist experienced in the management of dementia. After initiation of therapy, patients should be observed and drug treatment withdrawn if there is no response after 3 months. There has been development of specialised secondary care services to support the appropriate use of drugs for AD, in particular the establishment and further development of memory clinics.[13–15] It is likely that development will continue in the primary/secondary care interface around the management of early dementia as the number of potential treatments for dementia and the volume of research supporting diagnostic and therapeutic decisions increase. If initiation is restricted to specialist services, as recommended in various local guidelines for the use of drugs such as donepezil, there will be costs other than simply those of the drugs, such as memory clinics and specialist investigations, with an increase in referrals to neurological and psychiatric services. The scale of potential cost increase in such therapies is not known.

However, it can be argued that the introduction of assessment clinics should not be simply to select patients for drug treatment, but that all people with possible dementia deserve a proper diagnosis and assessment for prognosis. If this view were accepted, the costs of assessment clinics would not be wholly attributable to the use of anticholinesterase drugs. The average cost of memory clinics per patient attendance has been calculated to be £95 (see appendix 1).

The introduction of anticholinesterase drugs

Experience with the first acetylcholinesterase inhibitor (AChEI) to be licensed in the UK (donepezil) suggests that a small proportion of the theoretically eligible population (mild to moderately impaired) commence or continue treatment.* The use of drugs such as donepezil has been controversial. The North of England evidence-based guideline[16] recommended that:

- in the light of limited current knowledge, GPs should not initiate treatment with donepezil
- in the light of limited current knowledge, GPs should not continue hospital-initiated treatment with donepezil.

Melzer[17] reviewed the circumstances surrounding the launch of donepezil in the UK, and noted that the expectations of benefit raised by media coverage were not based on the available evidence, with exaggerated claims of both clinical and financial benefits. He notes also that the Alzheimer's Society sounded a note of caution about unrealistic expectations. Some initial advertisements for donepezil were considered to be misleading.[18–20]

The spectrum of services used by people with AD is broad and variable[21,22] (e.g. assessment and treatment, community support, respite care, financial help) and includes those shown in appendix 2.

* Unpublished data from one memory clinic in the South and West region show that 68% of patients referred commenced donepezil treatment, of whom only 50% remained on the drug around 9 months later

Reports from other Health Technology Assessment units

Most reports from other health technology assessment (HTA) units are now several years old, and relate to a time when donepezil and tacrine were the subject of review.

Trent Working Group on Acute Purchasing (December 1997)[8] concluded that:

> "Results of the trials showed modest improvement in cognitive function which were considered significant in research terms. It is unclear how much that improvement is translated into improvement in clinical functioning and quality of life for patients and carers.
>
> "Changes in clinical condition were reported using measures of global impression of change. However, these changes were minimal and the reliability of the scales has not been established."

Drug and Therapeutics Bulletin (August 1998)[23] noted that:

> "On the basis of the evidence available, we remain unconvinced of the value of donepezil in routine clinical practice."

Prescrire International (June 1998)[24] reported that:

> "Three comparative placebo-controlled trials are available, and show that the effects of donepezil are moderate and visible only on psychometric scales: the possible clinical benefit is unknown. In the long term, donepezil only delays cognitive deterioration by a few months."

A Wessex Development and Evaluation Committee (DEC) report (June 1997)[25] concluded that:

> "Results of the clinical trials show modest improvements in cognitive function as measured by two well validated scales (ADAScog and MMSE) and severity of disease measured using the Clinical Dementia Rating Scale. The clinical significance of these changes is uncertain. Changes in clinical condition were reported using measures of global impression of change. However these were minimal and reliability of the scales used has not been established. No definite changes in disability or quality of life have been demonstrated."

OSTEBA (The Basque HTA agency; 1998)[26] concluded that:

> "The current treatments available are not really found effective for the following reasons: the methodological problems found in the clinical trials undertaken up to now (sensitivity of the patient, measuring instruments, test instability, the selection of patients, the abandoning of treatment, blind study and reaction to placebo), the little improvement that has been seen and if this indeed continues over the long term."

NHS Northern and Yorkshire Regional Drug and Therapeutics Centre (February 1998)[27] reported that:

> "As yet, there is little evidence that treatment with donepezil has any impact upon other clinically relevant outcomes such as the ability to remain independent, likelihood of admission to residential/nursing care or to hospital or on overall quality of life. Only a half or less of patients show a clinically significant improvement in cognitive function; this declines when treatment is stopped. Some patients worsen despite treatment. Donepezil does not prevent pathological disease progression. Because of these limitations, donepezil cannot yet be generally recommended for treatment of dementia in mild to moderate AD."

The North of England evidence-based guidelines development project (1998)[16] stated:

> "Recommendations (grade of evidence)
>
> - In the light of limited current knowledge, general practitioners should not initiate treatment with donepezil (A)
> - In the light of limited current knowledge, general practitioners should not continue hospital initiated treatment with donepezil (A)."

Description of the interventions considered in this review

The three drugs considered in this review are all members of an expanding class of drugs, the AChEIs, which have been developed since recognition of the importance of reduced acetylcholine levels in the brain in the development of AD.[28] AChEIs act by inhibiting the enzyme responsible for metabolising acetylcholine in the hippocampus and cortex regions of the brain, thereby enhancing neurotransmitter levels, which may temporarily improve or stabilise some symptoms of the disease. Further effects on other elements in brain metabolism may also be relevant, although these have not been studied in detail.

Donepezil

Donepezil (Aricept, produced by Eisai Ltd and co-marketed with Pfizer) was licensed on 17 March 1997 and was the first drug to be licensed in the UK specifically for AD. Donepezil is administered once a day and is available in 5 mg and 10 mg preparations, the lower dose often being prescribed initially.

Donepezil must be used with caution in patients with sick sinus syndrome or other supraventricular conduction abnormalities, and in those at risk of developing peptic ulcers, asthma and obstructive airways disease.

Rivastigmine

Rivastigmine (Exelon, produced by Novartis Pharmaceuticals) was the second drug licensed in the UK specifically for AD and was launched in 1998. It is taken twice a day, starting with a low dose of 3 mg/day and increasing to between 6 and 12 mg/day.

Rivastigmine must be used with caution in patients with renal impairment, mild or moderate hepatic impairment, sick sinus syndrome, conduction abnormalities, gastric or duodenal ulcers and a history of asthma or obstructive pulmonary disease. Body weight should be monitored.

Galantamine

Galantamine is being developed by Janssen Pharmaceutica under a co-development and licensing agreement with UK-based Shire Pharmaceuticals Group, plc. A new drug application for galantamine has been filed by Janssen and is now under review by the US Food and Drug Administration (FDA).

Galantamine is a tertiary alkaloid originally isolated from snowdrop and narcissus bulbs.

Chapter 2
Methods

Methods used for the review

The *a priori* methods used for the review are outlined in the research protocol (see appendix 3); this was sent for expert comments to members of the advisory group for the review (see acknowledgements, page 41). Although many helpful comments were received relating to the general content of the research protocol, there were none that identified specific problems with the methods of the review.

Some changes, additions or points of clarification were made to the methods discussed in the original protocol.

- Originally limited to people suffering from mild to moderate AD, the inclusion criteria were broadened to include all patients with AD.
- In addition to comparisons between the three drugs and with placebo, the review would include studies that compared the drugs with other forms of care, such as rehabilitation and specialist clinics.
- It was suggested that study designs other than systematic reviews and randomised controlled trials (RCTs) should be included in the review. This was considered to be inappropriate since the aim of the review was to focus on clinical effectiveness, and good quality RCTs for donepezil, rivastigmine and galantamine were available.
- Abstracts and conference poster presentations of systematic reviews, RCTs and economic evaluations were excluded from the review. It was believed that these provided insufficient information on methods and results to judge accurately the rigour of the study and the reliability of the evidence presented.
- In addition to the key outcome measures assessing changes in cognition, function, behaviour and mood, and quality of life (QoL) (including studies assessing carer well-being and carer-input), the review would include studies reporting time to institutionalisation.
- The quality of economic evaluation studies would be assessed by their internal validity (i.e. the methods used) using a standard checklist,[29] and external validity (i.e. the generalisability of the economic study to the population of interest) using a series of relevant questions. Additionally, the reviewers would assess whether adjustments could be made to existing models to reflect the current situation in England and Wales.
- Economic results would be reported as base case to ensure comparability.
- Where appropriate, cost/QALY (quality-adjusted life-year) would be estimated by combining the following: effectiveness information from the trials; QoL information from the literature or consultation with experts; costs from published sources or, where appropriate and available, local NHS costs. If cost/QALY estimations were undertaken, sensitivity analysis would be performed to determine how robust estimates are to the assumptions made.

Sources of information, including databases searched and key search terms, can be found in appendix 4.

Studies identified by the search strategy were assessed for inclusion through three stages. Titles and abstracts of studies were screened independently for inclusion by two reviewers. The full text of those studies included at this stage was examined for inclusion by two reviewers. Data extraction and quality assessment of studies included in the review were undertaken by one reviewer and checked by a second reviewer. At each stage, any differences in opinion were resolved through discussion.

RCTs were assessed for quality using the Jadad scale[30] (see appendix 5) and systematic reviews were assessed for quality using the criteria developed by the NHS Centre for Reviews and Dissemination (CRD)[31] (see appendix 6).

Progression of AD is characterised by a worsening in the domains of cognition, functional ability, and behaviour and mood. Changes in one or more of these domains and their effect upon the patient's and the carer's well-being provide the basis for diagnosis, assessing severity and progression of the syndrome, and appraising the effectiveness of treatments. A wide range of measurement scales has been used in studies of the clinical effectiveness of treatments for AD. An overview of the main

measurement scales used in studies of donepezil, rivastigmine and galantamine for AD is shown in appendix 7.

A recent review[32] of measurement scales for AD raised concerns about the variety of measures that do not have adequate psychometric assessment. In addition, although many scales were considered reliable and valid, their responsiveness to change (effects of floors and ceilings on the measure), clinical meaning and relevance to patient and carer well-being remained unclear.

The diversity of these instruments, and the lack of consensus on the most appropriate measurement scales to use, necessarily determine the extent to which the effectiveness of the different treatments can be judged. It is evident that improvement in a limited set of outcome measures signifies an effect on the specific domains included, rather than a clinically meaningful and positive effect for patients and carers. The success or failure of treatments for AD should be evaluated over a broad rather than limited range of outcome measures. As such, this systematic review considered all outcomes reported in included studies.

Commercial-in-confidence data

Some data considered for this review were submitted in confidence. These commercial-in-confidence (CIC) data have been omitted from the results presented, as noted in italics in the following text.

Chapter 3

Clinical effectiveness

Donepezil

Quantity and quality of research for donepezil in AD

Three systematic reviews,[35–37] five published RCTs,[38–42] and four unpublished RCTs (*CIC data, not shown*), met the inclusion criteria for the review and are shown in *Table 4* and appendix 8.

All three systematic reviews were of good quality (CRD quality score, ≥ 4/6). One review[35] (eight RCTs) adequately stated its research question, search strategy, inclusion criteria, methods for and results of synthesis, and provided details of quality assessment of the included trials. The Wolfson review[36] (four RCTs) did not explicitly state inclusion or exclusion criteria, or discuss the method of application of criteria. The Livingston review[37] did not include assessment of the validity of studies or give sufficient details of the included studies, and only reported numbers-needed-to-treat (NNTs) derived from the literature.

Of the five published RCTs, two[39,42] were of very good quality (Jadad quality score, 5/5). The other three trials[38,40,41] were of good quality (Jadad quality score, 4/5), and the main methodological limitation was the lack of description of the method of randomisation. Four studies[38–41] had strict inclusion criteria, which may limit generalisability. The remaining study[42] had the inherent problems of a small crossover design, in particular no wash-out period between treatments which may influence results.

Three studies[39–41] compared two dosages of donepezil (5 mg/day and 10 mg/day) with placebo, one[38] was a dose-ranging study comparing donepezil 1, 3 and 5 mg/day with placebo, and the crossover study[42] used only donepezil 5 mg/day. Three studies were short-term, 6 weeks,[42] or 12 weeks followed by a wash-out period,[40] or 14 weeks.[38] Two studies reported results up to 24 weeks.[39,41]

The main primary outcome measures used in the studies include cognitive outcomes such as ADAS-cog, and global outcomes including CIBIC-plus or CGIC scales. Secondary outcomes were MMSE, CDR-SB (Clinical Dementia Rating Scale – Sum of the Boxes), ADL and physical and laboratory results.

CIC data for unpublished studies omitted.

Assessment of clinical effectiveness of donepezil in AD

All studies that gave details of treatment effects suggested that donepezil has a statistically significant beneficial effect on global and cognitive outcomes (e.g. CIBIC-plus and ADAS-cog) for people suffering from mild to moderate AD.

The three reviews[35–37] reported significant improvements in global outcome measures using CIBIC-plus scores. One review[35] reported greater improvement in CIBIC-plus for donepezil compared with placebo, with a Peto OR of 0.5 (95% CI, 0.3 to 0.7) for donepezil 10 mg/day and 0.5 (95% CI, 0.4 to 0.7) for donepezil 5 mg/day at 24 weeks. The Wolfson review[36] found that all of the donepezil trials reported a statistically significant difference between treatment and placebo groups using CIBIC-plus or CGIC, although the studies differed in the amount of detail reported, making direct comparison difficult.

Three trials[39–41] reported significant improvements in global outcome measures using CIBIC-plus scores. In one study,[40] mean score at 12 weeks was improved compared with placebo (placebo = 4.2 [standard error of mean, SEM, 0.07], donepezil 5 mg/day = 3.9 [SEM 0.08, $p = 0.003$], donepezil 10 mg/day = 3.8 [SEM 0.08, $p = 0.008$]), and in another[39] the difference in means at 24 weeks compared with placebo was reported as 0.36 for donepezil 5 mg/day ($p = 0.0047$) and 0.44 for donepezil 10 mg/day ($p < 0.0001$).

The percentage of patients showing clinical improvement (CIBIC-plus scores of 1, 2 or 3) with donepezil was reported in two studies, although it is not clear whether results reach statistical significance in one of them (32%, 38% and 18% for donepezil 5 mg/day, donepezil 10 mg/day, and placebo, respectively, at 12 weeks;[40] 21%, 25% and 14% for donepezil 5 mg/day, donepezil 10 mg/day, and placebo, respectively, at 24 weeks, $p < 0.05$[41]).

TABLE 4 *Summary of evidence of the effectiveness of donepezil in AD*

Author, year and study details	Global outcome measurements	Cognitive outcome measurements	Functional/QoL measurements	Adverse effects
Published systematic reviews				
Birks, *et al*., (2000)[35] *Design*: systematic review of 8 RCTs, 7 in meta-analysis *Intervention*: donepezil (any dose) with parallel, concomitant placebo control *Patients*: probable AD (details in appendix 8) *CRD quality score*: 6/6	*CIBIC-plus:* 12 weeks, 10 mg/day vs placebo, OR = 0.4 (95% CI, 0.2 to 0.6), Z = 3.89 24 weeks, 10 mg/day vs placebo, OR = 0.5 (95% CI, 0.3 to 0.7), Z = 4.15 12 weeks, 5 mg/day vs placebo, OR = 0.5 (95% CI, 0.3 to 0.8), Z = 2.81 24 weeks, 5 mg/day vs placebo, OR = 0.5 (95% CI, 0.4 to 0.7), Z = 3.67	*ADAS-cog (WMD)*: 12 weeks, 10 mg/day vs placebo = –3.1 (95% CI, –4.2 to –1.9), Z = 5.23 24 weeks, 10 mg/day = –2.9 (95% CI, –3.6 to –2.2), Z = 7.6 12 weeks, 5 mg/day vs placebo, = –2.3 (95% CI, –3.2 to –1.5), Z = 5.34 24 weeks, 5 mg/day = –1.9 (95% CI, –2.6 to –1.1), Z = 4.89	*PDS*: 52 weeks, 10 mg/day vs placebo = –3.8 (95% CI, –5.9 to –1.7), Z = 3.55 No evidence of difference in donepezil compared with placebo on patient-rated QoL scale at 12 or 24 weeks	Adverse reactions seen more frequently in the 10 mg donepezil group compared with the 5 mg group or placebo group were nausea, vomiting and diarrhoea
Wolfson, *et al*., 2000[36] *Design*: systematic review of one phase II and 3 phase III parallel, double-blind trials *Intervention*: donepezil vs placebo *Patients*: probable AD *CRD quality score*: 5/6	*CIBIC-plus treatment – placebo differences from Phase III trials:* RCT 1: 5 mg/day, 0.3 (p = 0.0326); 10 mg/day, 0.4 (p = 0.0009) RCT 2: statistically significant (no p values given) RCT 3: 5 mg/day, 0.36 (p = 0.0047); 10 mg/day, 0.44 (p < 0.001)	*ADAS-cog*: 5 mg/day vs placebo, ranging from –1.5 (p = 0.002) to –3.2 (p < 0.01) 10 mg/day vs placebo, –2.88 (p < 0.001) to –3.1 (95% CI, –4.22 to –1.92)	*QoL*: one trial found significant worsening due to donepezil 10 mg/day compared with placebo	Mild to moderate nausea, vomiting, diarrhoea; also dizziness, common cold, headache, flushing, agitation, pain, constipation, nasal congestion, cough, gastric upset, insomnia, rhinitis
Livingston, *et al*., 2000[37] *Design*: systematic review of 1 RCT on donepezil and 2 RCTs on rivastigmine, reporting NNTs *Intervention*: donepezil vs placebo *Patients*: probable AD *CRD quality score*: 4/6	*CIBIC-plus improvement ≥ 3:* 5 mg/day, NNT 7 (95% CI, 5 to 16) 10 mg/day, NNT 8 (95% CI, 5 to 19) *CIBIC-plus improvement ≥ 5:* 5 mg/day, NNT 9 (95% CI, 5 to 94) 10 mg/day, NNT 5 (95% CI, 4 to 11)	*ADAS-cog: no deterioration:* – 5 mg/day, NNT 5 (95% CI, 4 to 9) 10 mg/day, NNT 5 (95% CI, 3 to 8) *ADAS-cog improvement ≥ 4:* 5 mg/day, NNT 10 (95% CI, 5 to 180) 10 mg/day, NNT 4 (95% CI, 3 to 7) *ADAS-cog improvement ≥ 7:* 5 mg/day, NNT –15* (95% CI, –828 to 8) 10 mg/day, NNT 6 (95% CI, 4 to 12)		–

* *Recalculated for the present review (incorrectly reported in the review by Livingston,* et al.[37]*)*

continued

TABLE 4 contd *Summary of evidence of the effectiveness of donepezil in AD*

Author, year and study details	Global outcome measurements	Cognitive outcome measurements	Functional/QoL measurements	Adverse effects
Published RCTs				
Rogers, *et al*., 1996[38] *Design*: RCT, double-blind, multicentre, parallel-group, placebo-controlled. ITT analysis *Intervention*: donepezil 1 mg/day (*n* = 42), donepezil 3 mg/day (*n* = 40), donepezil 5 mg/day (*n* = 39), placebo (*n* = 40) for 14 weeks *Patients*: mild to moderate AD (*N* = 161) *Jadad quality score*: 4/5	*CGIC at 12 weeks:* most patients scores unchanged *Clinical improvement (CGIC score 1–4):* 5 mg/day, 89% placebo, 81%	*ADAS-cog – adjusted mean change from baseline (p value vs placebo):* placebo, 0.7 1 mg/day, –0.9 ($p = 0.105$) 3 mg/day, –1.4 ($p = 0.036$) 5 mg/day, –2.5 ($p = 0.002$) dose trend significant ($p < 0.04$) 38 weeks: results show average increase of 6.6 points/year compared with expected 11.6 points/year	*ADL*: adjusted mean change from baseline – no significant differences	Nausea, vomiting, dizziness, gastric upset and constipation in treatment groups and placebo Follow-up: additionally agitation, pain, UTI, common cold, URI, headaches, confusion, insomnia, accidents
Rogers, *et al*., 1998[39] *Design*: RCT, double-blind, multicentre, placebo-controlled. ITT analysis *Intervention*: donepezil 5 mg/day (*n* = 154), donepezil 10 mg/day (*n* = 157), placebo (*n* = 162) for 24 weeks *Patients*: mild to moderate AD (*N* = 473) *Jadad quality score*: 5/5	*CIBIC-plus, difference in means at 24 weeks:* 5 mg/day vs placebo, 0.36 ($p = 0.0047$) 10 mg/day vs placebo, 0.44 ($p < 0.0001$)	*ADAS-cog, difference in means at 24 weeks:* 5 mg/day vs placebo, –2.49 ($p < 0.0001$) 10 mg/day vs placebo, –2.88 ($p < 0.0001$) *Change from baseline compared with placebo at 24 weeks*: 5 mg/day, $p < 0.0001$ 10 mg/day, $p < 0.0001$	*QoL*: no differences between treatment groups	Incidence of fatigue, diarrhoea, nausea, vomiting and muscle cramps were all significantly greater in donepezil 10 mg goup than placebo group ($p \leq 0.05$)
Rogers, *et al*., 1998[40] *Design*: RCT, double-blind, multicentre, placebo-controlled. ITT analysis *Intervention*: donepezil 5 mg/day (*n* = 157), donepezil 10 mg/day (*n* = 158), placebo (*n* = 153) for 12 weeks *Patients*: mild to moderate AD (*N* = 468) *Jadad quality score*: 4/5	*CIBIC-plus mean score at 12 weeks:* placebo = 4.2 (± 0.07), 5 mg/day = 3.9 ($p = 0.003$) 10 mg/day = 3.8 ($p = 0.008$) *Clinical improvement (CIBIC-plus score 1, 2 or 3):* placebo = 18% 5 mg/day = 32% 10 mg/day = 38%	*ADAS-cog, least squares mean change from baseline:* placebo, 0.4 5 mg/day, –2.1 ($p < 0.001$) 10 mg/day, –2.7 ($p \leq 0.001$)	*QoL*: no significant difference between placebo and 5 mg/day 10 mg/day, significant worsening vs placebo, –4.3 ($p = 0.02$)	Donepezil 10 mg/day was associated with transient mild nausea, insomnia and diarrhoea

continued

TABLE 4 contd *Summary of evidence of the effectiveness of donepezil in AD*

Author, year and study details	Global outcome measurements	Cognitive outcome measurements	Functional/QoL measurements	Adverse effects
***Published RCTs* contd**				
Burns, *et al.*, 1999[41] *Design*: RCT, double-blind, multicentre, parallel-group. ITT analysis *Intervention*: donepezil 5 mg/day (n = 271), donepezil 10 mg/day (n = 273), placebo (n = 274) for 24 weeks *Patients*: mild to moderate AD (N = 818) *Jadad quality score*: 4/5	*Patients improved at 24 weeks (CIBIC-plus scores ≤ 3):* 5 mg/day, 21% 10 mg/day, 25% placebo, 14% ($p < 0.05$)	*ADAS-cog, differences in least square means for change from baseline to 24 weeks:* 5 mg/day vs placebo, 1.5 ($p = 0.0021$) 10 mg/day vs placebo, 2.9 ($p < 0.0001$)	*QoL:* no treatment effects noted	Nausea, diarrhoea, vomiting, anorexia, dizziness, confusion, insomnia, in both donepezil and placebo groups
Greenberg, *et al.*, 2000[42] *Design*: RCT, double-blind, two centre, placebo-controlled, crossover. Not ITT analysis *Intervention*: donepezil 5 mg/day (n = 30), placebo (n = 30) for 6 weeks *Patients*: probable AD (N = 60) *Jadad quality score*: 5/5	N/A	*ADAS-cog:* *Net improvement (estimated by combining within-individual changes during drug and placebo):* 2.17 (95% CI, 0.20 to 4.10) *Patients improved (score decreased):* donepezil, 44% placebo, 19% ($p = 0.03$)	N/A	Nausea, diarrhoea, agitation
Unpublished RCTs (CIC data, omitted)				
The Nordic Study	–	–	–	–
The Functional Study	–	–	–	–
The Nursing Home Study	–	–	–	–
The MSAD Study	–	–	–	–

ADAS-cog, Alzheimer's Disease Assessment Scale cognitive subscale; ADL, Uniform Activities of Daily Living; CI, confidence interval; CIBIC, Clinician's Interview-based Impression of Change; CGIC, Clinical Global Impression of Change; ITT, Intention-to-treat; N/A, not assessed; OR, odds ratio; PDS, Progressive Deterioration Scale; QoL, quality of life; URI, upper respiratory tract infection; UTI, urinary tract infection; WMD, weighted mean difference

Two reviews[35,36] found significant changes in cognitive function due to donepezil using the ADAS-cog outcome measurement scale. Greater improvement compared with placebo was reported as weighted mean differences of –2.9 (95% CI, –3.6 to –2.2) for donepezil 10 mg/day and –1.9 (95% CI, –2.6 to –1.1) for donepezil 5 mg/day at 24 weeks.[35] Improvement in cognition due to donepezil as measured by the ADAS-cog score was slightly greater in the 10 mg treated patients than in the 5 mg treated patients, but there were more withdrawals in the high-dose groups.[36]

Four of the five trials[38–41] showed significant changes in cognitive function using the ADAS-cog outcome measurement scale. Net improvement (estimated by combining within-individual changes during drug treatment and placebo) in ADAS-cog score was reported in the crossover study as 2.17 (95% CI, 0.20 to 4.10)[42] after 6 weeks treatment with donepezil (5 mg/day). After 12 weeks treatment with donepezil 5 mg/day, one study reported least squares mean change from baseline ADAS-cog score as –2.1 ($p < 0.001$)[40] and another reported mean drug–placebo difference as –2.5 (min –8.0, max 7.0, $p = 0.002$).[38] Difference in least square means for change in ADAS-cog from baseline to 24 weeks compared with placebo was reported as 1.5 for donepezil 5 mg/day ($p = 0.0021$) and 2.9 for donepezil 10 mg/day ($p < 0.0001$).[41] ADAS-cog difference in means at 24 weeks showed an improvement of 2.49 compared with placebo ($p < 0.0001$) for donepezil 5 mg/day and 2.88 ($p < 0.0001$) for donepezil 10 mg/day.[39]

The percentage of patients showing clinical improvement, defined as a decrease in ADAS-cog score, was reported as 44% with 5 mg/day donepezil and 19% with placebo ($p = 0.03$).[42]

A dose–response effect was reported, which demonstrated greater benefits for patients with donepezil 10 mg/day than with 5 mg/day, and with 5 mg/day compared with 3 or 1 mg/day.[38,39]

All studies reported no significant improvement due to donepezil in functional and QoL measurements. One study reported significant worsening due to 10 mg/day donepezil compared with placebo using a non-validated QoL scale (–4.3, $p = 0.02$).[40]

The review by Livingston[37] reported an NNT analysis and suggested that small numbers of patients (in most cases between five and eight) need to be treated with higher doses of donepezil for improvement on global and cognitive scales. The Livingston review[37] reported wide confidence limits for the lower dose of donepezil.

Adverse effects of donepezil were reported in most studies, but they are mainly mild and transient, and include nausea, vomiting and diarrhoea. More serious reactions were reported in two studies,[40,42] and include stomach ulcer with haemorrhage, syncope, generalised seizure, transient ischaemic attack, aphasia, tremor and diaphoresis.

CIC data for unpublished studies omitted.

Summary of the use of donepezil in AD

- The effects of donepezil compared with placebo have been considered in three systematic reviews and five RCTs (total, 1980 patients), and in four unpublished studies involving a further 1133 patients (*CIC data, omitted from this published report*).
- Published studies are of good or very good quality. (*Comments on unpublished studies omitted.*)
- Results suggest that donepezil is beneficial in AD patients with the mild to moderate form of the disease when assessed using global and cognitive outcome measurement scales. However, improvements on these scales are small and may not be clinically significant. The key question in all of the studies considered is whether the statistically significant differences seen mainly in sensitive cognitive measures such as ADAS-cog are accompanied by real changes that are meaningful to patients and their carers.
- Side-effects, such as nausea, vomiting and diarrhoea, are usually mild and transient.
- Generalisability of results may be restricted to particular patient groups (specifically to patients with the mild to moderate form of the disease with limited co-morbidity or concomitant interventions).

Rivastigmine

Quantity and quality of research for rivastigmine in AD

Three systematic reviews[36,37,43] and five RCTS,[44–48] and two unpublished RCTs (*CIC data, not shown*), met the review inclusion criteria and are summarised in *Table 5* with further details in appendix 9.

All three systematic reviews were of good quality. One review[43] adequately stated its research question, search strategy, inclusion criteria,

TABLE 5 *Summary of evidence of the effectiveness of rivastigmine in AD*

Author, year and study details	Global outcome measurements	Cognitive outcome measurements	Functional/QoL measurements	Adverse effects
Published systematic reviews				
Birks, *et al.*, 2000[43] *Design*: Systematic review of 7 RCTs, 2 unpublished *Intervention*: rivastigmine any dose vs parallel concomitant placebo control *Patients*: probable AD *CRD quality score*: 6/6	*CIBIC-plus (no change or worse at 26 weeks):* 6–12 mg/day vs placebo, OR = 0.7 (95% CI, 0.6 to 0.9), *Z* = 3.39 1–4 mg/day vs placebo, OR = 0.7 (95% CI, 0.6 to 0.9), *Z* = 2.47 2–12 mg/day, t.d.s. vs b.d., OR = 0.64 (95% CI, 0.42 to 0.98), *Z* = 2.06	*ADAS-cog change from baseline at 26 weeks:* 6–12 mg/day vs placebo = –2.1 (95% CI, –2.7 to –1.5), *Z* = 7.41 1–4 mg/day vs placebo = –0.8 (95% CI, –1.5 to –0.2), *Z* = 2.54 2–12 mg/day, t.d.s. vs b.d. = –1.3 (95% CI, –2.6 to 0.0), *Z* = 1.94	*PDS (WMD at 26 weeks):* 6–12 mg/day vs placebo = –2.2 (95% CI, –3.2 to –1.1), *Z* = 4.16 1–4 mg/day vs placebo = 0.4 (95% CI, –0.9 to 1.6), *Z* = 0.60	Not stated
Wolfson, *et al.*, 2000[36] *Design*: systematic review of 2 placebo-controlled, double-blind, multicentre trials of 26 weeks *Intervention*: rivastigmine vs placebo *Patients*: probable AD *CRD quality score*: 5/6	*Study 1, CIBIC-plus, change from baseline:* high dose, 0.2 (95% CI, 0.04 to 0.36) low dose, 0.23 (95% CI, 0.07 to 0.39) placebo, 0.49 (95% CI, 0.33 to 0.65) *Study 2, CIBIC-plus, mean score:* high dose, 3.91 (95% CI, 3.71 to 4.09) low dose, 4.24 (95% CI, 4.02 to 4.38) placebo, 4.38 (95% CI, 4.22 to 4.58)	*Study 1, ADAS-cog mean change:* high dose, 0.31 (95% CI, –0.46 to 1.08) low dose, 2.36 (95% CI, 1.59 to 3.13) placebo, 4.09 (95% CI, 3.32 to 4.86) *Study 2, ADAS-cog mean change:* high dose, 0.26 (95% CI, –1.06 to 0.66) low dose, 1.37 (95% CI, 0.53 to 2.27) placebo, 1.34 (95% CI, 0.41 to 2.19)	*PDS*: statistically significant differences between high-dose rivastigmine and placebo	Frequently reported (≥ 5%) for rivastigmine: fatigue, dizziness, somnolence, nausea, vomiting, anorexia, sweating, asthenia, dyspepsia, diarrhoea, abdominal pain, malaise
Livingston, *et al.,* 2000[37] *Design*: systematic review of 1 RCT on donepezil, 2 RCTs on rivastigmine, reporting NNTs *Intervention*: rivastigmine vs placebo *Patients*: probable AD *CRD quality score*: 4/6	*Study 1, CIBIC-plus improvement:* 1–4 mg/day, NNT = 10 (95% CI, 6 to 44) 6–12 mg/day, NNT = 6 (95% CI, 4 to 11) *Study 2, CIBIC-plus improvement:* 1–4 mg/day, NNT = 12 (95% CI, 6 to 273) 6–12 mg/day, NNT = –12.5 (95% CI, –179 to 6)	*ADAS-cog:* improvement ≥ 4 (1–4 mg/day), NNT = –10 (95% CI, –13 to 19) improvement ≥ 4 (6–12 mg/day), NNT = 13 (95% CI, 7 to 111) no deterioration, 6–12 mg/day, NNT = 4 (95% CI, 3 to 6) decline ≥ 4, 6–12 mg/day, NNT = 5 (95% CI, 3 to 8) decline ≥ 7, 6–12 mg/day, NNT = 5 (95% CI, 4 to 7)	N/A	N/A

continued

TABLE 5 contd *Summary of evidence of the effectiveness of rivastigmine in AD*

Author, year and study details	Global outcome measurements	Cognitive outcome measurements	Functional/QoL measurements	Adverse effects
Published RCTs				
Sramek, *et al*., 1996[44] *Design*: double-blind, parallel-group, safety/ tolerability Phase I RCT *Intervention*: 12 mg/day rivastigmine t.d.s. (*n* = 20), 12 mg/day rivastigmine b.d. (*n* = 20), placebo (*n* = 10) for 10 weeks *Patients*: probable AD (*N* = 50) *Jadad quality score*: 4/5	N/A	N/A	N/A	Headache, nausea, dizziness, diarrhoea, vomiting, flatulence, agitation, fatigue, abdominal pain, rhinitis, coughing, myalgia, urinary incontinence, dyspepsia, sweating, asthenia
Agid, *et al*., 1998[45] *Design*: RCT, double-blind, multicentre, placebo-controlled. Not ITT analysis *Intervention*: 4 mg/day rivastigmine (*n* = 136), 6 mg/day rivastigmine (*n* = 133), placebo (*n* = 133) for 13 weeks *Patients*: probable AD (*N* = 402) *Jadad quality score*: 4/5	*CGIC treatment success (scores 1 or 2):* 6 mg/day, 42.7% 4 mg/day, 31.5% placebo, 29.9% higher dose vs placebo, $p = 0.05$	*MMSE*: no significant differences	–	For both rivastigmine and placebo: nausea, vomiting, diarrhoea, abdominal pain, dizziness, headache
Corey-Bloom, *et al*., 1998[46] *Design*: RCT, double-blind, multicentre, placebo-controlled. ITT analysis *Intervention*: rivastigmine mean 3.5 mg/day (low dose, *n* = 233), rivastigmine mean 9.7 mg/day (high dose, *n* = 231), placebo (*n* = 235) for 26 weeks *Patients*: probable AD (*N* = 699) *Jadad quality score*: 5/5	*CIBIC-plus:* statistically significant improvement for high dose vs placebo, –0.29 (95% CI, –0.51 to –0.07; $p < 0.01$)	*ADAS-cog:* statistically significant improvement for high dose vs placebo, 3.78 (95% CI, 2.69 to 4.87; $p < 0.001$)	*PDS:* statistically significant improvement for high dose vs placebo, 3.38 (95% CI, 1.51 to 5.25; $p < 0.001$)	Significantly more common in high-dose group than placebo group in maintenance phase: dizziness, vomiting, dyspepsia

continued

TABLE 5 contd *Summary of evidence of the effectiveness of rivastigmine in AD*

Author, year and study details	Global outcome measurements	Cognitive outcome measurements	Functional/QoL measurements	Adverse effects
***Published RCTs* contd**				
Forette, *et al*., 1999[47] *Design*: RCT, double-blind, multicentre, placebo-controlled. Not ITT analysis *Intervention*: rivastigmine b.d., mean 9.6 mg/day (n = 45), rivastigmine t.d.s., mean 10.1 mg/day (n = 45), placebo (n = 24) for 18 weeks *Patients*: probable AD (N = 114) *Jadad quality score*: 2/5	*CIBIC-plus, patients improved (score 1, 2 or 3)*: rivastigmine b.d., 57% placebo, 16% p = 0.027	*ADAS-cog:* non-significant improvement on rivastigmine b.d. vs placebo, p = 0.054	–	Nausea, vomiting, dizziness, anorexia, headache in rivastigmine and placebo groups 4 serious adverse reactions in rivastigmine group – weight loss and hypersalivation, nausea and vomiting, bradycardia, and abdominal pain
Rosler, *et al*., 1999[48] *Design*: RCT, double-blind, multicentre, placebo-controlled. ITT analysis *Intervention*: rivastigmine mean 3.7 mg/day (low dose, n = 243), rivastigmine mean 10.4 mg/day (high dose, n = 243), placebo (n = 239) for 26 weeks *Patients*: probable AD (N = 725) *Jadad quality score*: 5/5	*CIBIC-plus, mean change from baseline*: high dose, 3.91 (95% CI, 3.71 to 4.09) low dose, 4.24 (95% CI, 4.02 to 4.38) placebo, 4.38 (95% CI, 4.22 to 4.58) high dose vs placebo, p < 0.001 *CIBIC-plus, patients improved (score 1, 2, or 3)*: high dose, 37% low dose, 30% placebo, 20% high dose vs placebo, p < 0.001 low dose vs placebo, p > 0.05	*ADAS-cog, mean change from baseline*: high dose, 0.26 (95% CI, –0.66 to 1.06) low dose, –1.37 (95% CI, –2.27 to –0.53) placebo, –1.34 (95% CI, –2.19 to –0.41) no significant differences *ADAS-cog, patients improved (≥ 4 points)*: high dose, 24% low dose, 15% placebo, 16% no significant differences	*PDS, mean change from baseline*: high dose, 0.05 (95% CI, –1.57 to 1.77) low dose, –3.37 (95% CI, –4.99 to –1.61) placebo, –2.18 (95% CI, –3.91 to –0.49) no significant differences	Significantly more common in high rivastigmine group than placebo: nausea, vomiting, dizziness, headache, diarrhoea, anorexia, abdominal pain, fatigue, malaise
Unpublished RCTs (CIC data, omitted)				
Novartis 2000	–	–	–	–
Novartis 2000	–	–	–	–

PDS, Progressive Deterioration Scale; b.d., twice-daily dosing; t.d.s., three-times-daily dosing

quality assessment of the included trials, and methods for and results of synthesis. The Wolfson review[36] (four RCTs) did not explicitly state inclusion or exclusion criteria, or discuss the method of application of criteria. The Livingston review[37] did not include assessment of the validity of studies or give sufficient details of the included studies, and only reported NNTs derived from the literature.

Two of the published RCTs[46,48] were of very good quality (Jadad quality score, 5/5) and included patients with co-existing disease and concomitant drug therapy, increasing general applicability of results. One good quality trial (Jadad quality score, 4/5)[45] lacked any description of the method of randomisation and used multiple outcome measures without stating which were primary and which were secondary outcomes. Another good quality trial[44] was a Phase I safety/tolerability trial which did not report the method of randomisation. The fifth study[47] was of poor quality (Jadad quality score, 2/5) and gave no details of the method of randomisation or blinding and no description of drop-outs.

All of the published studies included patients with mild to moderate and/or probable AD, and four out of the five used global outcome measurements such as CIBIC-plus and CGIC and cognitive outcomes such as ADAS-cog. One study used the QoL outcome PDS. The Phase I trial reported adverse events only. In the two very good quality trials, the doses of rivastigmine consisted of a low dose between 1 mg and 4 mg daily, with means of 3.5 mg/day[46] and 3.7 mg/day,[48] and a high dose between 6 mg and 12 mg daily, with means of 9.7 mg/day[46] and 10.4 mg/day.[48] Another study[45] used two doses, 4 or 6 mg/day, and the fourth trial[47] used increasing doses of rivastigmine from 2 to 12 mg/day to reach mean maximum tolerated doses of 9.6 mg/day in a twice-daily dosing regimen or 10.1 mg/day in a three-times-daily dosing regimen. Follow-up was for 13 weeks,[45] 18 weeks[47] and 26 weeks.[46,48] The Phase I trial[44] used rivastigmine 12 mg/day three-times-daily dosing or 12 mg/day twice-daily dosing with a 10-week follow-up period.

CIC data for unpublished studies omitted.

Assessment of clinical effectiveness of rivastigmine in AD

All RCTs reporting global outcome measurements showed significant improvements from baseline for higher doses of rivastigmine compared with placebo.

One review[36] revealed a moderate benefit on global clinical status from high-dose treatment with rivastigmine. A statistically significant effect as measured by CIBIC-plus was observed in both the included trials, and both studies included a heterogeneous mix of study participants. However, the review by Birks[43] reported benefits with higher doses of rivastigmine in CIBIC-plus, and significant differences in CIBIC-plus with lower doses at 26 weeks but not earlier.

In the published RCTs, CIBIC-plus score improved (decreased) by –0.29 (95% CI, –0.51 to –0.07; $p < 0.01$),[46] and mean change from baseline was 3.91 (95% CI, 3.71 to 4.09) for rivastigmine 10.4 mg/day compared with 4.38 (95% CI, 4.22 to 4.58; $p < 0.001$) for placebo.[48] The percentage of patients improved (CIBIC score 1, 2 or 3) was 57% with rivastigmine 9.6 mg/day (twice daily dosing) compared with 16% in the placebo group ($p = 0.027$) in one trial,[47] and 37% for rivastigmine 10.4 mg/day compared with 20% in the placebo group ($p < 0.001$) in another trial.[48] Treatment success (CGIC scores 1 or 2) was reported as 42.7% patients treated with 6 mg/day compared with 29.9% patients in the placebo group ($p = 0.05$).[45]

For cognitive outcome measures, both reviews that report results showed moderate benefit from rivastigmine treatment. One meta-analysis[43] revealed benefit as measured by change from baseline in ADAS-cog test scores compared with placebo at 26 weeks for both the higher dose of rivastigmine (–2.1; 95% CI, –2.7 to –1.5) and the lower dose (–0.8, 95% CI, –1.5 to –0.2). It should be noted that there was significant heterogeneity between the trials for the higher dose analysis as shown by the ADAS-cog analysis chi-squared test.

Among the four published RCTS that included cognitive outcome measures, one[46] reported statistically significant improvement on the ADAS-cog scale for 9.7 mg/day rivastigmine compared with placebo (3.78; 95% CI, 2.69 to 4.87; $p < 0.001$). Two trials[47,48] reported non-significant improvements on the ADAS-cog scale and the fourth[45] showed no significant differences in MMSE.

QoL measurements using PDS showed statistically significant improvements for 9.7 mg/day rivastigmine compared with placebo (3.38; 95% CI, 1.51 to 5.25; $p < 0.001$) in one trial[46] but non-significant improvement in another.[48] Both reviews[36,43] also showed improvement relative to placebo with the higher dose rivastigmine but not with the lower dose.

The review by Livingston[37] reported an NNT analysis and suggested that small numbers of patients (in most cases between three and seven) need to be treated with appropriate dosages of rivastigmine to ameliorate the clinical symptoms of AD or postpone deterioration in one of them.

The most frequent adverse effects reported in the trials were nausea, vomiting, diarrhoea, headaches, dizziness, abdominal pains, fatigue and malaise.

CIC data for unpublished studies omitted.

Summary of the use of rivastigmine in AD

- The effects of rivastigmine compared with placebo have been considered in three systematic reviews and five published RCTs (total, 1990 patients), and in two unpublished studies involving a further 1380 patients (*CIC data, omitted from this published report*).
- All but one of the published studies are of good or very good quality. (*Comments on unpublished studies omitted.*)
- Results suggest that rivastigmine is beneficial in patients with AD in terms of global outcome measurements. Statistically significant cognitive and functional improvements are not reported in all studies. Improvements on these scales may not be clinically significant.
- Adverse effects include nausea, vomiting, diarrhoea, headaches, dizziness, abdominal pain, fatigue, malaise, anxiety and agitation.
- Generalisability of the results may be limited to patients with mild to moderate AD.

Galantamine

Quantity and quality of research for galantamine in AD

One review[36] and three RCTs,[49–51] and three unpublished RCTs (*CIC data, not shown*), met the inclusion criteria for the review. The RCTs are summarised in *Table 6* and appendix 10.

The systematic review[36] found no trials of galantamine in AD.

Two published trials of galantamine[50,51] were of very good quality (Jadad quality score, 5/5), with details of methods of randomisation and blinding, and full trial profiles showing numbers of patients who dropped out. One trial[50] assessed galantamine at three doses, 8, 16 and 24 mg/day, and the other trial[51] considered two doses, 24 mg/day and 32 mg/day. Patient characteristics and inclusion and exclusion criteria were similar for both trials. Primary outcome measures were the ADAS-cog and CIBIC-plus scores and length of follow-up was 5 or 6 months. One study[51] was continued as an open-label extension for another 6 months, but detailed results are not given. The third published trial,[49] a Phase II RCT, was of poor quality (Jadad quality score, 1/5). It was not described as double-blind and gave no details about randomisation or withdrawals/drop-outs. Results were reported only in graph form. Three doses of galantamine were used, 22.5, 30 and 45 mg/day, and follow-up was for 12 weeks.

CIC data for unpublished studies omitted.

Assessment of clinical effectiveness of galantamine in AD

Both good quality RCTs showed significant improvements in cognitive and global function from baseline for higher doses of galantamine compared with placebo. The poor quality Phase II study showed improvement in cognitive function only, at one dose only.

In one trial, the proportion of patients shown to be stable or improved using the CIBIC-plus scale was significantly ($p < 0.001$) higher in the 16 mg/day group (66%) and the 24 mg/day group (64%) compared with the placebo group (49%).[50] The other trial reported results as the proportion of patients with CIBIC-plus scores markedly, moderately or minimally improved, or with no change, or minimally, moderately or markedly worsened. Both doses of galantamine (24 mg/day and 32 mg/day) produced a better outcome than placebo ($p < 0.05$).[51]

The galantamine–placebo differences in ADAS-cog were 3.1 points for both the 16 mg/day group and 24 mg/day group ($p < 0.001$) in one study.[50] The treatment effects of galantamine compared with placebo on the ADAS-cog scale in the other good quality study were 3.9 points for 24 mg/day and 3.4 points for 32 mg/day ($p < 0.001$ for both galantamine groups versus placebo).[51] Mean change from baseline in ADAS-cog was 0.875 in the 30 mg/day galantamine group compared with –2.5 in the placebo group in the poor quality study ($p = 0.008$).[49]

Compared with the placebo group, the galantamine 16 mg/day and 24 mg/day groups had a significantly better outcome on ADL. Mean (SEM) change from baseline for placebo was –3.8 (0.6), compared with –0.7 (0.5) and –1.5 (0.6) for groups treated with galantamine 16 or

TABLE 6 *Summary of evidence of effectiveness of galantamine in AD*

Author, year and study details	Global outcome measurements	Cognitive outcome measurements	Functional/QoL measurements	Adverse effects
Published RCTs				
Wilcock, *et al*., 1997[49] *Design*: randomised, placebo-controlled, safety and efficacy Phase II RCT. ITT analysis *Intervention*: 22.5 mg/day galantamine (*n* = 83), 30 mg/day galantamine (*n* = 54), 45 mg/day galantamine (*n* = 54), placebo (*n* = 62) for 12 weeks *Patients*: probable AD (*N* = 253) *Jadad quality score*: 1/5	N/A	*ADAS-cog: mean change from baseline score at 12 weeks (ITT analysis) (estimated from graphical display):* placebo, –2.5 (95% CI, –4.25 to –0.875; *p* = ns) 22.5 mg/day, –1 (95% CI, –2.75 to 0.75; *p* = ns) 30 mg/day, 0.875 (95% CI, –0.75 to 2.625; *p* = 0.008) 45 mg/day, –0.25 (95% CI, –2 to 1.5; *p* = ns)	N/A	Nausea, vomiting
Tariot, *et al*., 2000[50] *Design*: double-blind, placebo-controlled, multicentre RCT. Not ITT analysis *Intervention*: 8 mg/day galantamine (*n* = 140), 16 mg/day galantamine (*n* = 279), 24 mg/day galantamine (*n* = 273), placebo (*n* = 286) for 5 months *Patients*: probable AD (*N* = 978) *Jadad quality score*: 5/5	*CIBIC-plus, proportion of patients stable/improved*: placebo, 49% 8 mg/day, 53% (ns vs placebo) 16 mg/day, 66% (vs placebo, *p* < 0.001) 24 mg/day, 64% (vs placebo, *p* < 0.001)	*ADAS-cog: mean (SEM) change from baseline*: placebo, 1.7 (0.39) 8 mg/day, 0.4 (0.52); ns vs placebo 16 mg/day, –1.4 (0.35); vs placebo, *p* < 0.001 24 mg/day, –1.4 (0.39); vs placebo, *p* < 0.001	*ADCS/ADL mean (SEM) change from baseline*: placebo, –3.8 (0.6) 8 mg/day, –3.2 (0.8); ns vs placebo; 16 mg/day, –0.7 (0.5); vs placebo, *p* < 0.001; 24 mg/day, –1.5 (0.6); vs placebo, *p* < 0.01	Nausea, vomiting, anorexia, agitation, diarrhoea
Raskind, *et al*., 2000[51] *Design*: double-blind, placebo-controlled, multicentre RCT. Not ITT analysis *Intervention*: 24 mg/day galantamine (*n* = 212), 32 mg/day galantamine (*n* = 211), placebo (*n* = 213) for 6 months *Patients*: probable AD (*N* = 636) *Jadad quality score*: 5/5	*CIBIC-plus score (1 = markedly improved; 2 = moderately improved; 3 = minimally improved; 4 = no change; 5 = minimally worsened; 6 = moderately worsened; 7 = markedly worsened), proportion by score:* placebo: 1 = 0.5; 2 = 3.6; 3 = 9.7; 4 = 42.9; 5 = 30.6; 6 = 12.2; 7 = 0.5 24 mg/day: 1 = 1.6; 2 = 3.2; 3 = 15.1; 4 = 53.2; 5 = 19.4; 6 = 5.4; 7 = 2.2 (vs placebo, *p* < 0.01) 32 mg/day: 1 = 1.2; 2 = 2.3; 3 = 12.3; 4 = 53.2; 5 = 25.1; 6 = 5.3; 7 = 0.6 (vs placebo, *p* < 0.05)	*ADAS-cog, mean (SEM) change from baseline*: placebo, 2.0 (0.45) 24 mg/day, –1.9 (0.36); vs placebo, *p* < 0.001 32 mg/day, –1.4 (0.44); vs placebo, *p* < 0.001	*DAD score*: no significant difference in mean change	Nausea, vomiting, anorexia, dizziness, diarrhoea, weight loss, abdominal pain, tremor

continued

TABLE 6 contd *Summary of evidence of effectiveness of galantamine in AD*

Author, year and study details	Global outcome measurements	Cognitive outcome measurements	Functional/QoL measurements	Adverse effects
Unpublished RCTs (CIC data, omitted)				
Wilcock, *et al.*, 2000	–	–	–	–
Rockwood, *et al.*, 2000	–	–	–	–
Wilkinson, *et al.*, 2000	–	–	–	–
ADCS, Alzheimer's Disease Cooperative Study; DAD, Disability Assessment for Dementia scale				

24 mg/day, respectively ($p < 0.001$ and $p < 0.01$, respectively).[50] No significant differences were found in mean change in total DAD score.[51]

Adverse effects included nausea, vomiting, anorexia, agitation, dizziness, diarrhoea, weight loss, abdominal pain, agitation and tremor. Most events were mild in severity.

CIC data for unpublished studies omitted.

Summary for the use of galantamine in AD

- The effects of galantamine compared with placebo have been considered in three published RCTs (1614 patients) and in three unpublished studies involving a further 1324 patients (*CIC data, omitted from this published report*).
- Two of the published trials are of very good quality and one is of poor quality. (*Comments on unpublished studies omitted.*)
- Results suggest that galantamine is beneficial in patients with AD in terms of global, cognitive and functional scales. Statistically significant results are reported in both good quality trials. The clinical significance of these improvements is not clear. (*Comments on unpublished studies omitted.*)
- The most common adverse effects were predominantly gastrointestinal and most events were mild.
- Generalisability may be limited to people with mild to moderately severe AD.

Chapter 4

Economic evaluation

Approach for reviewing economic evaluation literature

The aim of this section of the review was to assess the existing economic evaluation evidence for donepezil, rivastigmine and galantamine in the symptomatic treatment of AD. If this evidence could be judged to be sufficient, it would be possible to inform NHS decision-makers about the likely economic impact of prescribing these drugs. However, it is frequently the case that, given the early stage in the development of new drugs, the best available cost-effectiveness information is based on decision-analytic models. These models must be carefully appraised as they use observed and modelled data from multiple secondary sources to build a (hopefully) coherent analysis. Unfortunately, their biggest drawback is that they can be prone to biases. A good model requires relevant structure, data, and extrapolation methods, but beyond that, there is no consensus in the literature about how to achieve this.[52] Thus any attempt to assess a model is a judgement made on the part of the review team. It is possible to adjust a model if more suitable data become available, but much harder to adjust a structurally flawed model or one that is poorly reported. Full access to the model is necessary to update or adjust it to suit local or national requirements.

The review was carried out from an NHS perspective. However, where the evidence suggested there might be important costs falling on carers or other non-NHS organisations, or benefits for carers, these were noted.

The review of economic evaluation studies is reported in three sections. The first sets out key background details pertaining to each of the studies, including a brief summary of the cost-effectiveness results and the assessments made of internal and external validity. The second section makes reference to the device known as the cost-effectiveness plane to explain in some detail the results of the one study considered most generalisable to the current situation in England and Wales. The third section provides a breakdown of the plethora of sectors currently involved in financing the care of people with AD in England and Wales. It also discusses some possible sources of more up-to-date resource and cost information. In addition, it considers the drug prescribing costs and issues. These three sections are followed by our overall conclusions about the economic evaluations of donepezil, rivastigmine and galantamine in England and Wales.

Some data considered for this review were submitted in confidence. These CIC data have been omitted from the results presented here.

Quantity and quality of research available on cost-effectiveness

Papers in English were retrieved using the search strategy shown in appendix 4 to identify economic evaluations. This yielded five studies that, based on the abstract, met the inclusion criteria (see appendix 3). Subsequently, four further studies were identified from more recently published journals and reports. Of the nine studies, five compared donepezil with placebo or usual care[25,54–57] and four compared rivastigmine with placebo,[58–61] although one[59] of these was a cost-savings model that was used in two of the other studies.[60,61] There were no studies found for galantamine. Key characteristics of each study are summarised in *Tables 7* and *8*.

Summary of cost-effectiveness of donepezil and rivastigmine

Table 9 describes the key cost-effectiveness results and provides commentary on the interpretation of those results. However, as analysts have used different methods and studies are from different countries of origin, these studies cannot be closely compared.

Donepezil

The five studies of donepezil produced a variety of estimates; in two studies base-case estimates were cost saving, with dominant cost-effectiveness ratios (i.e. a cost saving and an increased effectiveness). However, in the remaining three studies base-case estimates were more costly with incremental cost-effectiveness ratios (ICERs) (i.e. an additional cost for an increase in effectiveness).

TABLE 7 *Characteristics of donepezil economic evaluation studies*

	Economic evaluation study no.				
	1	**2**	**3**	**4**	**5**
Author	Stein,1997[25]	Stewart, *et al.*, 1998[54]	Jonsson, *et al.*, 1999[55]	O'Brien, *et al.*, 1999[56]	Neumann, *et al.*, 1999[57]
Publication year	1997	1998	1999	1999	1999
Base-year prices	?	?1996 or 1997	?1995 (drugs 1998)	1997	1997
Intervention	Donepezil 5 mg/day, 10 mg/day, placebo	Donepezil 5 mg/day, 10 mg/day, placebo	Donepezil 5 mg/day, 10 mg/day, placebo	Donepezil 5 mg/day, usual care (no tacrine)	Donepezil **pooled** 5 and 10 mg daily doses, placebo
Study type	CUA by simple calculation	CEA model (Markov)	CEA model (Markov)	CEA model (decision analysis and Markov)	CUA model (Markov)
Study group	Mild/moderate AD	Mild/moderate AD	Mild/moderate AD	Mild/moderate AD	Mild/moderate AD
Perspective	Health sector	Societal (carers, health and social care sectors)	Health and social care sectors	Societal (carers, health and social care sectors)	Societal (carers, health and social care sectors)
Industry role	None	Collaborator	Funder – no disclaimer reported	Funder – investigators full publishing control	Funder – investigators full publishing control
Country of origin	UK	UK	Sweden	Canada	US

Note '?' means unclear information reported

CEA, cost-effectiveness analysis; CUA, cost–utility analysis

When sensitivity analyses were taken into consideration, estimates fluctuated more widely and there were, in some cases, conflicting results for sub-group analyses (e.g. by severity or drug dose). Such variations cast doubt on the robustness of the estimates.

Rivastigmine

The four rivastigmine studies are more difficult to interpret due to their manner of presentation. The oldest UK study[58] was based on information that is now out of date (further effectiveness data have since become available) and used simple modelling techniques that have been surpassed by the more recent fuller economic evaluations.[59–61]

The UK cost-savings study[59] presented full results for the high-dose group (currently recommended UK dosage) only. Among groups of patients with mild or moderate AD, there were average cost savings per patient treatment lasting from 6 months to 3 years, but they were 'insignificant' until after 2 years of treatment. Results varied according to anticipated life expectancy and the time period considered. Interpretation of the results is difficult due to the exclusion of drug therapy costs. Cost-effectiveness ratios could not be extracted as the associated effectiveness was not reported.

The above model[59] was used in the two subsequent studies.[60,61] However, these studies did not present ICERs even where they could have been calculated. Furthermore, the US study[60] did not present an overall (mean) effectiveness. Excluding drug costs, average total cost savings for the trial population were minimal at 6 months and increased over the 2 years, although savings for sub-groups (mild or moderate at baseline) varied according to the time horizon chosen.

The Canadian study[61] found the delay in disease progression was minimal at 6 months but increased

TABLE 8 *Characteristics of rivastigmine economic evaluation studies*

	Economic evaluation study no.			
	6	**7**	**8**	**9**
Author	Stein, 1998[58]	Fenn & Gray, 1999[59]	Hauber, *et al.*, 2000[60]	Hauber, *et al.*, 2000[61]
Publication year	1998	1999	2000	2000
Base year prices	?	1997	1997	1997
Intervention	Rivastigmine dose applicable to results unclear (1–12 mg/day), placebo	Rivastigmine (1–4 and 6–12 mg/day doses), placebo	Rivastigmine (dose not specified, but 1–4 and 6–12 mg/day doses in RCTs), placebo	Rivastigmine (across all doses: 1–4 and 6–12 mg/day), placebo
Study type	CUA by simple calculation	Cost savings model* (survival analysis, patient data)	CEA model (survival analysis, patient data)	Cost–consequence analysis (survival analysis, patient data)
Study group	Mild/moderate AD	Patients with varying severity AD	Mild/moderate AD	Mild/moderate AD
Perspective	Health sector	Health and social care sectors	?	Societal
Industry role	None	Funder – no disclaimer reported	Funder – no disclaimer reported	Funder – no disclaimer reported
Country of origin	UK	UK	US	Canada

* *Included here as model was basis for Hauber studies*[60,61]

Note ? means unclear information reported

over 2 years. There were average net costs (including the expected drug cost) at both 6 months and 1 year, but a cost saving at 2 years. The authors also estimated the QALY gains (for combined patient and carer) that would be required for a threshold cost per QALY using two arbitrary levels.

Internal validity

Appendix 11 shows the tables summarising the assessment made of internal validity for the nine studies. Seven of the studies appear from what is reported to have achieved acceptable standards of internal validity. Where debatable issues are of concern, these are potentially rectifiable by re-modelling, assuming better data are available and the model is accessible. The other two studies[25,58] did not seem to achieve acceptable standards of internal validity (full details are shown in appendix 11, pages 108–113). General points arising from this review are discussed below.

Comparator

As each study compared donepezil or rivastigmine with placebo, the studies can only inform the question of drug treatment versus 'no treatment' (i.e. placebo or usual care), not which drug offers best value.

Furthermore, effectiveness estimates were obtained from RCTs conducted internationally, most of which included few if any UK-based patients. Thus, it is not possible to ascertain whether 'real usual care' in the UK is significantly different from the baseline care measured in these studies and therefore the applicability of the reported ICERs.

Perspective

If the NHS is the only perspective of interest, then some costs and benefits that are included when a societal perspective is taken will not be relevant; but this could be misleading. It would seem the important cost driver is the potential ability to forestall entry into more dependent (and thus more costly) forms of long-stay accommodation. In England and Wales the current finance of long-term care is extremely fragmented (i.e. financed by NHS, Social Services, Local Authorities, Benefits Agency, and out-of-pocket payments) with only a small proportion funded by the NHS.

TABLE 9 *Cost-effectiveness results: donepezil and rivastigmine*

Results	Study authors' interpretation
Donepezil	
Study 1[25] *Base case*: no single base case presented *Sensitivity analysis*: included only drug treatment costs – all results were ICERs (cost per QALY)	*Conclusion*: caution since the limits of the cost–utility were broad *Caveats*: • CUA rested on assumptions regarding validity of cognitive performance as a measure of disease progress and likely duration of disease • No definite evidence of improved effectiveness of 10 mg over 5 mg daily dose, although side-effects dose-dependent • Several cost elements not included
Study 2[54] *Base case*: compared with placebo, ICERs < £10,000 per year in non-severe state for both mild and moderate groups at both donepezil doses. Change from 5 to 10 mg/day donepezil, ICER < £5000 for mild group, but no incremental benefit for moderate group *Sensitivity analysis*: majority of results were increased costs for increased effectiveness and relative positions were unchanged • Moderate group: greater spread of results than mild group and no incremental benefit for 5 mg/day compared with 10 mg/day • Lower mortality rate reduced cost-effectiveness slightly • Discount rate (comparisons vs placebo). Lower rates (0% and 3%) – increased ICERs (mild or moderate); decreased ICERs for 5 vs 10 mg/day for mild group. Higher rate (10%) – decreased ICERs	*Conclusion*: drug treatment almost cost neutral and favours either 5 or 10 mg/day donepezil *Caveats*: • Modelling, therefore caution (since cost data from different patient group compared with RCT) • Delaying entry to residential homes shifts the care burden onto informal carers • If treatment reduces mortality, patients spend longer in a state of suffering from, albeit less severe, dementia
Study 3[55] *Base case*: dominant (cost saving, increased effectiveness) *Threshold analysis:* • Drug cost (equal to cost of care savings) separately for 5 mg/day and 10 mg/day • Drug effectiveness 33% and 45% for 5 and 10 mg/day, respectively *Sensitivity analysis*: • Discounting costs decreased net costs (increased savings) • Varying annual drug cost: 5 mg/day varied between net cost saving and cost; 10 mg/day remained cost saving • Effectiveness (30%–70%): both doses varied between net costs and cost savings • Donepezil treatment was cost saving even when patients switched to no-treatment probabilities after the first cycle • Within-trial analysis produced best case – large cost savings and increased effectiveness. Worst case was an incremental cost (overall effectiveness not reported) using a lower drug effectiveness	*Conclusion*: both dosages dominant with 5 mg/day donepezil the most cost-effective *Caveats*: • Results should be viewed as preliminary • Results realistic and applicable in Sweden • Patients in model had dementia (proportion with AD unknown) and were younger than in the RCT • Results driven by observed correlation between MMSE score and cost of care that cannot be confirmed without naturalistic trials

continued

TABLE 9 contd *Cost-effectiveness results: donepezil and rivastigmine*

Results	Study authors' interpretation
***Donepezil* contd**	
Study 4[56] *Base case*: dominant (cost saving, increased effectiveness) *Sensitivity analysis*: all scenarios, except continuing treatment when in the severe state, produced cost savings and increased effectiveness • Baseline severity: MMSE 21–26 ICER, whereas MMSE 15–20 and 10–14 were both dominant (savings and effectiveness were greater for MMSE 15–20) • Increased survival rates (25–100%) increased savings (and effectiveness) • Discounting (0–7%) reduced savings and effectiveness • Continuing (5 mg/day) donepezil when MMSE < 10 produced the worst case with an ICER • Monthly (not quarterly) dispensing fees produced smaller savings • Alternative aggregation weights increased cost savings • Care-giver time valued at average rather than minimum wage – modest reduction in cost saving	*Conclusion*: best estimate, donepezil saves money and improves outcomes, and so is economically attractive from broad perspective *Caveats*: • Limitations of data (e.g. assumptions about distribution of patients between MMSE groups) • Cost impact spread over several health and non-health budgets • Improved ways of valuing care-giver time needed • Markov models difficult to validate • When to stop drug treatment (i.e. MMSE < 10) and frequency of dispensing are important
Study 5[57] *Base case*: ICERs (cost per QALY) for both mild/community and moderate/community groups at start *Sensitivity analysis*: two scenarios produced cost savings while the remainder had a wide range of ICERs • ICERs were larger when considering direct costs alone • Results were sensitive to the duration of drug effect (< 18 months) and drug cost (i.e. varied between cost saving and ICER) • Results were somewhat sensitive to rates of disease progression and rates of discontinuation of treatment • Results were insensitive to preference weights, discount rate, and rate of nursing home placement	*Conclusion*: cost-effectiveness ratios higher in moderate AD and highly sensitive to duration of donepezil treatment and effect *Caveats*: • Results should be viewed as speculative • Results underscore uncertainty of results • Useful to identify gaps – lack of long-term efficacy data, costs, QoL, nursing home placement information • Societal perspective – donepezil may reduce some nursing home costs at the expense of the unpaid care-giver • Payers should be cautious about interpreting results for their own settings
Rivastigmine	
Study 6[58] *Base case*: no single base case presented *Sensitivity analysis*: presented as either costs a) including only drug treatment costs or b) including some non-drug treatment costs – all results were ICERs (cost per QALY) for between 1 and 5 years treatment	*Conclusion*: caution re interpreting results, which were uncertain *Caveats*: • Particular uncertainties were the appropriate duration of treatment, effect on QoL and carers, cost-effectiveness and organisational impact on the NHS
Study 7[59] *Base case*: **excluding drug costs**, both mild and moderate groups on high-dose rivastigmine had average cost savings per patient from 6 months to 3 years. Cost savings were not 'significant' until at least 2 years treatment and were affected by anticipated life expectancy. The sub-group achieving the highest cost savings varied according to time period considered *Sensitivity analysis*: none	*Conclusion*: depending on the cost of drug therapy, care savings may reduce the net costs to levels acceptable to decision-makers *Caveats*: • Analysis is a possible approach to estimating cost savings from AD treatment • Link between disease progression and economic events (e.g. entry to nursing home) only available by calculation using secondary sources • Caution about extrapolating beyond the trial sample and duration

continued

TABLE 9 contd *Cost-effectiveness results: donepezil and rivastigmine*

Results	Study authors' interpretation
***Rivastigmine* contd** **Study 8**[60] *Base case*: results not aggregated for study population or applied to local population – therefore overall average effectiveness not presented Results presented for baseline mild and moderate groups – both had minimal delay in progression (mild to moderate and subsequently moderate to severe) over 6 months. Delay in progression more at 1 and 2 years (less than 1 month and up to approx. 4 months maximum for some groups, respectively) **Excluding drug costs**, savings from delayed cognitive decline presented for mild and moderate baseline cohorts. Average total cost savings for trial population were minimal at 6 months, increased at 1 year, but were most at 2 years. Savings for sub-groups (mild or moderate at baseline) vary according to time horizon chosen *Sensitivity analysis*: none	*Conclusion*: rivastigmine delays disease progression for patients with mild/moderate AD and decreases the costs of caring through delaying the probability of institutionalisation *Caveats*: • Conclusions about cost savings depend upon life expectancy of each cohort – not incorporated into model • Cost savings at 6 months may have been under-estimated due to way disease progression stages defined (and due to need to cross thresholds to incur increased costs) • Model does not allow for improvements in MMSE • Caution in use of results in cost-benefit calculations – costs[62] derived from relatively small sample of AD patients in one area of California
Study 9[61] *Base case*: results presented for baseline mild, mild/moderate, moderate groups, and all stages. No ICER presented. For all stages: • Delay in progression minimal at 6 months, approx. 1 month at 1 year and approx. 4.5 months at 2 years • **Excluding drug costs**, average daily cost savings minimal at 6 months, increase at 1 year and highest at 2 years • Average net costs (including expected drug cost) at both 6 months and 1 year, but cost saving at 2 years • Threshold cost per QALY (for combined patient and carer) analysis using two arbitrary levels (Can$20,000 and 100,000). QALY gained required for thresholds varied according to baseline severity (i.e. cost saving for mild and all stages), and relatively small changes (< 0.092) required for mild–moderate and moderate levels *Sensitivity analysis*: none	*Conclusion*: savings exceed treatment costs after 2 years treatment for cohort of patients with mild AD. Gains in QoL may be of equal or greater value to society than net costs of treatment *Caveats*: • Modelling – only estimates reduction in costs of care attributable to delayed disease progression • Relationship between disease progression and well-being not clear – hence calculation of threshold values • Conclusions about cost savings depend upon life expectancy of each cohort – not incorporated into model • Model does not include impact of people withdrawing from treatment • Model uses pooled drug doses, although it is likely that more of the higher dose will be prescribed (with associated improved effectiveness, but no increase in costs) • Caution since results extrapolated beyond 1 year and no data available to validate

In this context, to understand the full economic impact of the drug therapies is a complex task. In order to make informed decisions, it is important to highlight other sectors affected (see page 29). Any recommendation to introduce AChEIs for the treatment of AD can shift cost burdens between sectors. However, the costs and benefits of drug therapy falling on specific budget holders cannot be properly understood from the way data are reported currently because the level of disaggregation is inadequate. In particular, it is worth highlighting that the delay in institutionalisation may increase the informal care-giver burden due to additional costs, while the effect on their QoL is unknown, and that a short delay in a move to residential care may not in real life produce any significant savings – the place may just be taken by another patient.

Duration of effect

It was apparent that a key uncertainty in the economic models was duration of effect. The clinical

evidence measured a short period (24–26 weeks therapy) but consequences were rolled out over a longer time frame. Apart from Neumann,[57] who used expert views to judge the duration of effect, the basis for this roll-out was unclear. The other studies extrapolated therapy to 5 years for donepezil and up to 3 years for rivastigmine. As yet, there is no evidence to support benefit of that duration of treatment of AD, and the natural history of this progressive disease makes it unlikely. Clearly, a shorter time frame generates lower cost savings and greater potential for positive net costs.

Sensitivity analysis

Sensitivity analysis is important to assess the robustness of cost-effectiveness results. It relies upon the analyst making good judgements about selecting the key parameters to be tested and their ranges of values. Preferred practice is to use multi-way or threshold analyses to understand the combined influence of variables on results. In this review it was found that most analysts reported limited sensitivity analysis confined to one-way analyses. In three studies[59–61] there was no sensitivity analysis. Additionally, some studies only considered two or three variables and gave no clear justification for their selection.[25,54,55,58] Two studies[56,57] discussed a wider array of variables, pinpointing important issues not raised by the other studies (e.g. drug price and dispensing cost; drop-out rate).

Side-effects

In the trials,[39,46,48] donepezil and rivastigmine treatment were associated with greater numbers of withdrawals than placebo. Except in the Neumann study,[57] withdrawals were omitted from the economic analysis. At this time it is unknown what the magnitude and direction of the economic consequences of side-effects and adherence to treatment are likely to be.

Economic evaluation outcomes used and QoL effect

Six of the economic evaluations used the MMSE to model outcomes. However, as discussed in appendix 7, MMSE was not designed to measure subtle aspects of cognition and may be insensitive to changes. Therefore it is not an ideal outcome measure either in trials or for use in modelling.

Since both MMSE and the CDR scale (used in one study[57]) focus on cognition, they are not ideal for modelling QoL since they do not encompass other medical, emotional or social conditions.

QoL may be affected for both patients and carers. Although AChEIs might improve patients' and carers' QoL, it is also possible that an extended period of less severe AD might adversely affect QoL for either group. In the latter case, overall effectiveness is reduced and thus an unadjusted ICER would be more favourable than the quality-adjusted ICER. Furthermore, estimation of QALYs is problematical in this context as there is concern that QALY measurement may be inappropriate because of patients' cognitive impairment. Neumann[57] attempted to measure patient QALYs using carers as proxies but such measurements may inaccurately reflect the impact of AD on the patient or society.

At present, there is simply inadequate research available to understand the QoL impact and thus any economic modelling on this issue ought to be regarded cautiously.

Quality of modelling exercise

It is often difficult to judge the quality of the modelling exercise from journal publications, particularly because there are often reporting restrictions and lack of access to the models themselves. Higher quality is associated with techniques that minimise four sources of bias: framing of the model; model construction; reliability of estimates used; and the way sensitivity analysis is performed.[63] On this basis, two studies[56,57] appeared to be the most robust. An example of a potential bias was the assumed link between disease progression (through cognitive decline) and economic events (e.g. entry to nursing home). There was no direct evidence for donepezil or rivastigmine decreasing the care-giving cost or delaying entry into nursing homes. This was estimated using secondary data sources, usually from cohort studies associated with, but not from, the exact patient group of interest.

The study by Fenn[59] is a higher quality model as it uses individual patient data. However, unfortunately, the full range of UK results was not presented. The US and Canadian studies were based on this model, but they do not investigate the uncertainty in results by either sensitivity analysis or statistical tests for patient-based data.

External validity (generalisability)

A study can be internally valid, but the setting may not adequately reflect the key parameters for the local or national population of interest. This may arise for many reasons, including

differences in the type of patients or the delivery of care. For this reason it is recommended that the reviewer or user of economic findings examines the evidence for its transferability to the context of interest.[64] We have examined external validity by considering five relevant aspects.

However, forming an overall opinion about the studies in terms of both generalisability and internal validity can be difficult if faced with a study that scores well on one criterion and not the other. Our assessment of external validity for each of the studies is summarised in appendix 11 (page 114). General points arising from this review are presented below.

Patient group
Effectiveness obtained from trial evidence is likely to be overestimated due to the highly selective patient group(s) and the nature of participation in trials.

Relevance of setting
As an England/Wales perspective is sought, the four UK-based studies[25,54,58,59] are possibly more useful, but on the basis of the information reported we believe their internal validity should be judged more circumspectly.

Treatment
When should treatment stop? It can be difficult in practice to determine the level of disease progression at which to withdraw treatment. It is unclear what impact patients' withdrawing from treatment by not taking their prescribed medication (i.e increasing cost without any effect) might have outside the trial population.

Resource costs
Importantly, resource use and cost data for the more robust UK-based studies[54,59] were based on relatively old data (i.e. from the 1980s) that probably do not accurately reflect current patterns of service provision (see page 29).

Cost-effectiveness plane

Results are presented on a cost-effectiveness plane to locate and understand study findings more easily. By convention, a cost-effectiveness plane shows changes in effectiveness along the horizontal axis and changes in cost on the vertical axis.[65] It divides into four quadrants, labelled in clockwise sequence. If an intervention compared with a relevant alternative falls into quadrant I it means that the intervention is regarded as more costly and more effective. Quadrant II represents dominant interventions, that is, the intervention is both lower in cost and more effective. Quadrant III represents lower cost but with lower effectiveness, and quadrant IV shows dominated options (i.e. the intervention is comparatively far more costly and less effective). If study findings fall into either quadrant II or IV the economic decision is clear (i.e. a dominant intervention is more efficient, a dominated intervention is inefficient). If study findings fall into either quadrant I or III a value judgement is required by the relevant decision-maker.

Acceptability threshold levels can be used to help decision-makers and can be represented on the diagram as cut-off lines emanating from the origin. These levels are set exogenously. For example, it had been the practice for the South and West Region's DEC to use two arbitrary 'cut-off' lines at costs per QALY of less than £3000 and more than £20,000.[66] These thresholds, when combined with a grading of the quality of research evidence, guided recommendations as to whether treatments should be recommended. As an illustration, we have used these acceptability thresholds in the cost-effectiveness plane for donepezil from the UK economic study[54] (but for years in non-severe states rather than QALYs).

Uncertainty in the ICER results can move estimates into other quadrants or across an acceptability threshold. By representing the variation in results on the cost-effectiveness plane, the decision-maker can assess relative efficiency and the level of certainty of their decisions.

Interpretation of UK studies

The mean cost-effectiveness results of the Stewart[54] study are presented on a cost-effectiveness plane in *Figure 1.* Results are presented for mild AD and moderate AD groups at both doses, compared with placebo. Other UK studies could not be presented because the older ones[25,58] are based on information that is now out of date (further effectiveness data have since become available) and have used simple modelling techniques that have been surpassed. Unfortunately, the reported data in the remaining UK study[59] did not allow results to be presented on the cost-effectiveness plane.

Based on the cost-effectiveness plane,[65] the acceptability thresholds described above have

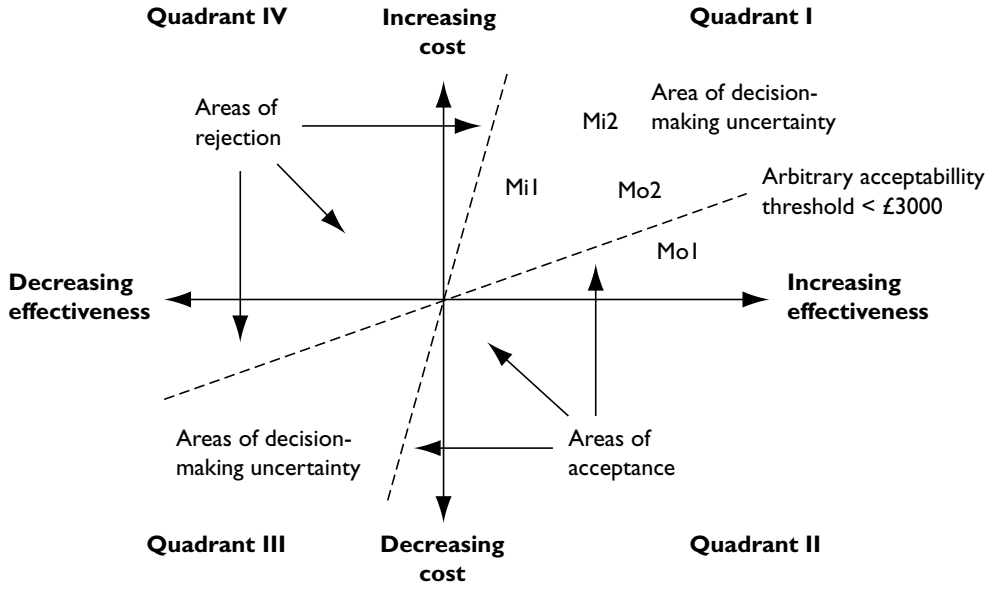

FIGURE 1 *Cost-effectiveness plane for donepezil in UK (from Stewart,* et al.*, 1998 study[54])*

been used to demarcate potential areas of decision-making classified as acceptable (i.e. close to or below the lower threshold), unacceptable (i.e. above the upper threshold) and uncertain (i.e. between the two thresholds).

All the results fell into quadrant I (i.e. more costly and more effective). Results for mildly affected patients fell into the area 'uncertain', with a lower ICER for the 10 mg dose of donepezil. However, the treatment of moderately affected patients appeared to be more cost-effective at the 5 mg dose (falling into the area 'acceptance'), whereas the 10 mg dose results fell into the area 'uncertain'. In each case the study's sensitivity analysis (not shown here), although very restricted, did not shift results into other quadrants or across a threshold.

However, interpretation of these results is complex. They appear to be illogical, with the most cost-effective alternative being 10 mg for the mildly affected group in contrast to 5 mg for the moderately affected group. In reality, accurate differentiation between mildly and moderately affected patients may be difficult outside a study population. Since the study did not present results for a combined mild + moderate group at each dose it is difficult to draw conclusions on which dose offers the best value for money.

Costing considerations in the treatment of AD

Identifying cost burdens

Evaluation of any new treatment should take into careful consideration who will bear the costs of treatment and who will gain the benefits. The chosen perspective will determine which sectors of society are included in the analysis. In AD, unravelling the relevant sectors is complex. Drug therapy costs are attributable to the healthcare sector, but potentially the greatest impact is in the social and informal care sectors. Sometimes this may lead to unexpected shifts in cost or care burdens between sectors. For example, the Canadian study[56] suggested that, compared with placebo, the cost of care-giver time might be greater for those treated with donepezil and decrease when the patient is admitted to an institution.

Transferring these findings to an England and Wales setting is not straightforward since patients and carers often pay for a considerable proportion of the care whether institutionalised or not. For example, in the UK, clients' and social security transfer payments accounted for more than 75% of costs for patients with advanced cognitive impairment in private households and private/voluntary residential or nursing homes.[67] (Note, though, that this proportion is based on relatively old data.)

Separating the various budget contributions is further complicated due to overlapping service provision and funding by different agencies. In addition, the balance between statutory agencies responsible for financing care for the elderly has dramatically changed since the 1980s (when much of the England/Wales published data were collected), with a shift away from NHS inpatient care and towards residential and nursing homes.[68] While home-help contact hours have also increased, community nursing services have barely increased.[68] The balance continues to change. For example, Local Authority residential care for older people is contracting, whereas overall Local Authority residential care is still expanding.[69] Furthermore, since 1995, there has been joint commissioning and provision by health and social care agencies. Such resource use patterns and volumes are changing rapidly so that they are likely to vary considerably within England and Wales.

Table 10 shows a breakdown of sectors or components in England and Wales involved in caring for people with AD. This illustrates the many

TABLE 10 *Sectors involved in caring for people with AD*

Expenditure item	Source of funding
Assessment and treatment, including monitoring (medical and social)	
GP visits	NHS
Hospital inpatient services (short/long term and mental health)	NHS
Hospital outpatient services (including elderly care/medical, memory clinics, and mental health e.g. liaison psychiatry)	NHS
Day hospital	NHS
Domiciliary visit (GP or consultant)	NHS
Social services (social worker)	SS
Health visitor, district nurse, incontinence nurse, community psychiatric nurse, speech therapist, occupational therapist, physiotherapist, chiropody, clinical psychologist	NHS, SS
Drug costs	NHS, private
Community support	
Meals on wheels	SS, VO, private
Bathing/dressing (nursing)	NHS, SS, private
Home care (e.g. home help, care assistant)	SS, VO, private
Transport	NHS, SS, LA, VO, private
Long-term residential care	
Assisted/sheltered accommodation (e.g. warden-supervised)	SS, LA, VO, private
Residential homes (Part III)	SS, VO, private
Nursing homes	SS, VO, private
Long-stay NHS wards (including psychiatric)	NHS
Respite care	
Day hospital	NHS
Day care	SS, LA, private
Respite admissions (hospital, nursing home, residential home)	NHS, SS, LA, private
Sitter services	SS, VO, private
Benefits	
Cash payments	Benefits Agency
Other	
Other personal expenses, contributions to the above and unpaid care-giver time	Private
Productivity losses	Private

Notes

NHS = NHS via health authority or regional funding; LA = local authority; SS = social services. Note boundaries between LA and SS depend on the locality (i.e. unitary authorities typically cover both roles)

VO = voluntary organisation (including housing associations)

In addition, it is now possible for NHS and local authority organisations to set up joint budgets to provide services

areas that may be affected by decisions about implementing any new treatment.

Treatment using AChEIs may involve additional costs in terms of patient assessment, actual treatment costs and follow-up (including monitoring for benefits or side-effects). In terms of economic evaluation, it is only the additional costs incurred beyond 'usual' care that are of interest.

In principle, it is important to recognise the additional cost impact of such drug prescribing. However, the situation is unclear due to varying patterns of service delivery. For example, memory clinics may be an important component, but these are currently financed in an *ad hoc* manner, often with pharmaceutical company support. There is no guarantee that the current pattern of care represents what will happen in the future.

For the reasons discussed in this section, the issue in costing drug therapies for AD is not just the drug cost *per se*, but the impact on different sectors, and the reality of achieved savings. Delaying admission to residential care may reduce costs in that sector (if beds are closed, rather than used for other people) but may increase community costs. Concentrating on the potential extra costs incurred by the NHS will ignore possibly adverse impacts on other sectors. For information, the costs of donepezil and rivastigmine are shown on page 32.

Availability of new cost information

Possible sources of recent resource use or cost information available

As discussed previously (pages 27–28), estimates of resource use and unit costs used in the published economic evaluations were based on relatively old data. Searching for more up-to-date information relevant to England and Wales is a large task that was outside the scope of this review. However, some professionals working in the field (see acknowledgements, page 41) were contacted to identify new sources of readily available information that would allow more up-to-date modelling. Examples of requirements for new data (specifically for people with AD) identified were: the proportion of people in different types of accommodation (living in the community, residential or nursing homes, since 1993); the proportion of people who fund their own residential or nursing home place; relative funding by Social Services, Local Authority, and NHS; number of carers of 'working' age who are in full-time work, or who, because of their caring commitment, work part-time or are unable to work.

It was possible to source new information this way which could be explored or used for secondary analysis, although it was not possible to do so at the time. Therefore, it is not possible to comment on the relevance of these sources to any future modelling exercise for people undergoing treatment with AChEIs.

Possible sources of new information include the following.

- Netten, *et al.* (1998): 1996 survey of care homes for the elderly people. Final report, Discussion paper 1423/2 PSSRU. This contains information about funding and cognitive impairment of nearly 11,000 residents in residential and nursing homes (although not specifically patients with AD).
- Local epidemiological surveys of people with dementia living alone (e.g. Gospel Oak survey).
- Department of Health – may have more up-to date information on continuing care.
- Alzheimer's Society publications:
  - *No accounting for health* (publication on budgets for dementia)
  - *The needs of people with dementia and those who care for them* (December 1999)
  - *Right from the start* (on the proportion of carers over 70 years old)
- *Part of their lives* by Jo Moriarty and Sarah Webb (The Policy Press, 2000)
- *Better for the break* by Enid Levin, Jo Moriarty and Peter Gorbach (NISW, 1994) – for proportion of carers who are partner/spouse, daughters, aged > 65 years, or in paid employment.
- Royal Commission on Long Term Care: policy options for informal carers of elderly people by L Pickard (1999) in *Long term care – rights and responsibilities*, Research Volume 3 Cm4192-II/3. TSO: London. (pages 22–25; 43–49) (not specific to AD).
- General Household Survey or the Family Resources Survey – for general information on carers.
- The RIS MRC CFAS (Resource Implications Study of Medical Research Council Cognitive Function and Ageing Study) included mentally frail people and collected economic data on carers, including the impact of care-giving on employment. Re-analysis of the data is possible. References to this work:
  1. McNamee P, *et al.* (1999). Costs of formal care for frail older people in England: the resource implication study of the MRC cognitive function and ageing study

(RIS MRC CFAS). *Social Science and Medicine* **48**:331–41.
2. RIS MRC CFAS (1998). Mental and physical frailty in older people: the costs and benefits of informal care. *Ageing and Society* **18**:317–54.
- Economists Advisory Group survey of carers of people with AD (1997).

AD2000 trial** – possible future source of new resource use or cost information (donepezil)

The AD2000 trial should provide important new information on the effectiveness and cost-effectiveness of donepezil for patients in England. AD2000 is a pragmatic RCT of treatment with donepezil compared with placebo. An economic evaluation is being conducted alongside the trial. Perspectives adopted are both societal and public sector, with collection of data on both formal and informal resource use to enable 'cost-shifting' to be explored. Treatment duration is for a maximum of 60 weeks, the main follow-up planned is up to 66 weeks, and by flagging patients' medical notes patients are being followed up until their death.

Recruitment will be completed by the end of 2001. The economic evaluation and modelling analyses beyond the trial period are:

- based on trial data alone
- modelled by extrapolation until the deaths of the patients.

Both analyses will be performed for the period up to 66 weeks and again up to 3 years.

The trial is being conducted in England with the obvious advantage that the setting and treatment will better reflect those of interest to the NHS. Furthermore, entry criteria are less restrictive than for previous RCTs and so the patient group should be more representative of 'typical' patients.

Primary outcome measures are:

- increase in disability, as defined by either loss of two basic activities of daily living (i.e. dressing, eating, washing and using the toilet) and/or loss of six of eleven instrumental activities of daily living
- the requirement for formal domiciliary or residential/nursing home care.

Secondary end-points, including important economic outcomes are:

- progress to severe cognitive impairment (MMSE < 10)
- activities of daily living (Bristol ADL Scale)
- presence and severity of non-cognitive neuro-psychiatric symptoms (Neuropsychiatric Inventory, NPI)
- formal and informal time spent by care-givers (probably using a hybrid of the Caregiver Time Survey and Caregiver Activity Survey)
- carer psychological well-being (General Health Questionnaire, GHQ-30)
- death from AD
- safety
- compliance (numbers stopping treatment because of side-effects, lack of perceived effectiveness or other reasons).

EQ-5D (EuroQoL) utility scores are being collected for a sub-sample of trial patients. The researchers intend to use multivariate statistical methods to estimate individual patient utility scores from the battery of outcome measures, to enable cost–utility analysis.

Other data on resource use to be collected (every 3 months) will include drug treatment, outpatient attendances, GP consultations, hospital admissions, and other formal/voluntary care. When possible the researchers intend to validate the data from carer interviews with other sources.

Drug costs and prescribing issues for donepezil, rivastigmine, and galantamine in England and Wales

Table 11 shows the costs to the NHS of prescribing the new AChEIs. These costs are for GP and hospital prescribing, excluding dispensing costs. Whereas the total budget for dispensing via community pharmacists is fixed (irrespective of the number of items dispensed), hospital dispensing costs vary according to local pharmacy services.

GP and hospital prescribing costs are attributable to different budgets within the NHS and vary according to the costing and reimbursement procedures. For example, GP prescribing does not incur VAT, unlike hospital prescribing. The costs in *Table 11* have been calculated using list prices (*British National Formulary*, BNF[70]). It should be noted that whereas GP prescribing costs are likely to be fairly standard, contract prices negotiated by hospitals for drugs may be considerably lower than the BNF price.

* Note that senior members of the NCCHTA have acted as *ex officio* members of the AD2000 trial steering committee.

TABLE 11 *Drug costs for donepezil, rivastigmine and galantamine in England and Wales*

Per patient at 2000 prices*	Monthly BNF[70] price (excl. VAT)	GP cost (BNF as not in Drug Tariff) less standard Prescription Pricing Authority discount 10%		Hospital cost with VAT (excl. dispensing)	
		Monthly	Annual	Monthly	Annual
Donepezil					
5 mg (28 day pack)	£68.32	£61.49	£799	£80.28	£1044
10 mg (28 day pack)	£95.76	£86.18	£1120	£112.52	£1463
Rivastigmine					
All (1.5 mg, 3 mg, 4.5 mg and 6 mg) doses (56 caps)	£63.00	£56.70	£737	£74.03	£962
Galantamine	Not currently available				

* *364 days = 13 packs of 28 days*

The cost of private prescription of these drugs was not investigated.

Conclusion about economic evaluations of donepezil, rivastigmine and galantamine

Nine available economic evaluation studies of new drug therapies used to treat AD were reviewed. This section summarises the overall results of the economic evaluations and draws conclusions about the available evidence and issues raised from this review. As discussed in the '*Summary of cost-effectiveness of donepezil and rivastigmine*' (page 21), these studies cannot be closely compared.

The five studies of donepezil produced a variety of cost-effectiveness estimates. Whereas the base cases showed increased effectiveness and were cost saving in two studies, they were more costly in the other three. When sensitivity analyses are taken into consideration estimates fluctuated more widely, and there were, in some cases, conflicting results for sub-group analyses. Such variations cast doubt on the robustness of the estimates.

The four rivastigmine studies are more difficult to interpret due to their manner of presentation. The oldest UK study[58] has been surpassed by more recent economic evaluations. Cost-effectiveness ratios in two studies[59,60] could not be extracted as the associated overall effectiveness was not reported and interpretation of the costs results alone is difficult due to the exclusion of drug therapy costs. The Canadian study[61] found average net costs within the first year, but a cost saving at 2 years, but it was not clear whether the data presented could be translated into ICERs.

No published economic evaluations of galantamine were found and the possible future cost of the drug (when licensed in England and Wales) was unavailable.

From this rapid review we conclude that there is great uncertainty surrounding the cost-effectiveness of these drug therapies. Specific issues arising during the review are summarised below.

- Cost implications of prescribing AChEIs are uncertain. The main issue is not drug costs *per se*, but the impact across different sectors. This remains unclear since the financing and provision of care for patients with AD in England and Wales is complex and difficult to unravel without dedicated resources to do so. The key cost driver is the drugs' potential ability to forestall entry into institutional care. However, in the studies, this was modelled using progression of cognitive decline (MMSE and CDR), with no direct evidence that institutional care is forestalled. In addition, shifting cost or care burdens between sectors may result in no net benefit, or some sectors (e.g. carers) might be adversely affected.
- It was possible to model the impact of the drugs on cognitive decline, although the MMSE (used in six of the studies) is not a good outcome measure to use when attempting to detect subtle changes. However, the link between cognitive decline and QoL is less clear, particularly since both the patients and their carers may be

affected. Similarly, the link between measures of functional ability and behaviour/mood and QoL are unclear. The ongoing AD2000 trial will probably provide important new information on these issues.

- Primary research is required into whether or how QALYs can be calculated in people with cognitive impairment since this is a contentious issue compounded by the fact that carers may be poor proxies. For these reasons, cost/QALY estimations were not attempted. The very modest benefits seen in the trials imply that any such cost would be high.
- Potential savings from short-term decreases in long-term care may not be realisable unless they lead to closure of beds or reduction in the number of homes. Such changes seem unlikely in the nursing home sector.
- To improve generalisability and decrease uncertainty in results from the existing models by re-modelling data requires access to the original models and is in itself a major investment of research effort. Although preliminary consideration of possible sources of more up-to-date data is discussed in the section on the availability of new cost information, there remains great uncertainty over many aspects (e.g. the duration of drug effect). For this reason, and those raised in the points above, such re-modelling was outside the scope of this review.

Chapter 5

Comments and conclusions

Implications for other parties

If drugs such as donepezil, rivastigmine and galantamine were effective in delaying institutionalisation, they would have an impact on patients, their carers and other parties. If drug therapy stabilised some of the symptoms of early to middle stage AD for even a limited period of time, QoL of carers may be affected, possibly adversely. There would be continued need for support from the wide range of agencies which currently supply services for patients and their carers, which would have financial implications.

Factors relevant to NHS policy

The most important factor in planning drug treatment for dementia is whether the drugs have benefits that are sufficient to justify the costs. There are many other competing uses of NHS funds for dementia, such as support for carers (day care, night-sitters, respite care). The increasing numbers of the very elderly will increase demands on services. On the basis of the current evidence, there is doubt about the cost-effectiveness of these drugs. However there is considerable demand for their use, and at present health authorities have taken different decisions on funding. It is highly desirable to develop a common position across the country.

Conclusions

Statement of principal findings

The main findings of this rapid review of donepezil, rivastigmine and galantamine for AD are summarised below.

Donepezil

There is evidence from studies using global and cognitive outcome measurement scales that donepezil may be beneficial in AD. However, improvements on these scales are small and may not be clinically significant. There is inconclusive evidence of effectiveness on functional ability and behaviour/mood. Adverse effects associated with donepezil, such as nausea, vomiting and diarrhoea, are usually mild and transient. The five economic studies of donepezil produced a variety of cost-effectiveness estimates. Although the base cases showed increased effectiveness and were cost saving in two studies, they were more costly in the other three. When sensitivity analyses are taken into consideration, estimates fluctuated more widely, and there were, in some cases, conflicting results for sub-group analyses. Such variations cast doubt on the robustness of the estimates. The reality of savings is doubtful.

Rivastigmine

Rivastigmine may be beneficial in patients with AD in terms of global outcome measurements. Statistically significant improvements on cognitive and functional scales are not reported in all studies. Improvements on these scales may not be clinically significant. Adverse effects include nausea, vomiting, diarrhoea, headaches, dizziness, abdominal pain, fatigue and malaise. The four economic studies of rivastigmine are difficult to interpret due to their manner of presentation. The oldest study has been surpassed by more recent evaluations. Cost-effectiveness ratios in two studies could not be extracted because the associated overall effectiveness was not reported and interpretation of the costs results alone is difficult due to the exclusion of drug therapy costs. The fourth study found average net costs within the first year, but a cost saving at 2 years, but it was not clear whether the data presented could be translated into incremental cost-effectiveness ratios.

Galantamine

Galantamine may be beneficial in patients with AD in terms of global, cognitive and functional measurements, particularly at higher doses. Clinical significance of improvements in these scales is not clear. Adverse effects include mild gastrointestinal events. No published economic evaluations of galantamine were found and the possible future cost of the drug (when licensed in England and Wales) was unavailable.

Strengths and limitations of the review

The rapid review has certain strengths, including the following.

- This systematic review is independent of any vested interest.
- The systematic review brings together the evidence for the effectiveness of three drugs for AD and an economic evaluation, applying consistent methods of critical appraisal and presentation.
- The review was guided by the principles for undertaking a systematic review. Before undertaking the rapid review, the methods of the review were set out in a research protocol (appendix 3), which was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods used to undertake the different stages of the review.
- An advisory group has informed the rapid review from its initiation, through the development of the research protocol and completion of the report.

In contrast, there were certain limitations placed upon the review.

- Due to time restrictions placed upon the review and differences in the design, duration, outcome measures and reporting of studies, synthesis of the included studies was through narrative review with no formal meta-analysis.
- Another restriction placed upon the review due to time constraints was the lack of follow-up with authors of studies to clarify whether all of the studies identified for inclusion in the review were in fact separate. In view of this, it is not possible to say if some of the study groups are the same or whether there is any overlap.
- The systematic review included both systematic reviews of RCTs and reports of individual RCTs. Although it was suggested that observational studies would provide useful additional information, it was considered that the included study designs provided the most appropriate, unbiased evidence for assessing clinical effectiveness. Clinical effectiveness studies reported only as abstracts are listed in appendix 12 and studies excluded from the review are listed in appendix 13.
- The quality of the RCTs was assessed using the Jadad scale.[30] Although the Jadad scale includes key elements by which to assess the quality of RCTs, including randomisation, blinding and withdrawals/drop-outs, it could be criticised for excluding other elements that may cause bias (e.g. not including the level of withdrawal/drop-out). It has also been pointed out that the Jadad scale "gives more weight to the quality of reporting than to actual methodological quality."[71]

Other issues

- Studies of the clinical effectiveness of donepezil, rivastigmine and galantamine have tended to focus on global (e.g. CIBIC-plus, CGIC and MMSE) and cognitive outcome measures (e.g. ADAS-cog), although measures of function, QoL, and behaviour and mood have been assessed (see *Table 12*). No doubt the focus on global and cognitive outcome measures reflects the US FDA's requirement to include these outcomes as primary measures of effectiveness.
- When assessed on one or more global and cognitive outcomes measures, donepezil, rivastigmine and galantamine have tended to show significant benefit to people with AD. Of the five published RCTs on donepezil, four assessed global outcomes and all assessed cognitive outcomes. All of the published studies showed significant benefit on at least one measure.* Of the five published RCTs on rivastigmine, the four studies that included a global outcomes measure and two of the four that assessed a cognitive measure found significant benefit.* Similarly, the three published studies on galantamine showed benefit to people with AD in two of three RCTs assessing global outcome measures and all three RCTs examining cognitive measures.*
- The effect of donepezil, rivastigmine and galantamine on functional and QoL measures and behaviour and mood was not as clear. Although four donepezil studies included a functional or QoL measure, only three of the studies showed significant benefit to patients and one study showed significant negative effects.* One of two published studies on rivastigmine and one of two published studies on galantamine assessed functional and QoL outcomes and found significant benefit.* The limited use of QoL measures, whether directed at the person with AD or their carers, is thought to reflect the relative infancy of these measures and the difficulty in developing a valid and reliable measure.[32] Research is underway to evaluate current methodology and to develop a new responsive instrument to measure health-related QoL in people with dementia. An NHS Research and Development HTA project entitled 'Measurement of health

* Discussion of unpublished studies (CIC data) omitted

TABLE 12 *Summary of the quality of studies and the effectiveness of donepezil, rivastigmine and galantamine on outcomes measures for AD*

Reference	Quality score	Method of analysis	Global outcome measures	Cognitive outcome measures	Functional and QoL measures	Behaviour and mood outcome measures	Other outcome measures
Donepezil							
Rogers, *et al.*, 1996[38]	4/5	LOCF	CGIC (+) CDR (ns)	ADAS-cog (+) MMSE (ns)	ADL (ns) QoL (ns)	N/A	N/A
Rogers, *et al.*, 1998[39]	5/5	LOCF	CIBIC (+) CDR (+)	ADAS-cog (+) MMSE (+)	QoL (ns)	N/A	N/A
Rogers, *et al.*, 1998[40]	4/5	LOCF	CIBIC (+) CDR (ns)	ADAS-cog (+) MMSE (+)	QoL (–)	N/A	N/A
Burns, *et al.*, 1999[41]	4/5	ITT	CDR (+)	ADAS-cog (+)	IDDD(+) QoL (ns)	N/A	N/A
Greenberg, *et al.*, 2000[42]	5/5	OC	Care-giver rated global impression (ns)	ADAS-cog (+) Verbal Memory/ Fluency (ns)	N/A	N/A	N/A
Nordic Study*	–	–	–	–	–	–	–
Functional Survival Study*	–	–	–	–	–	–	–
Nursing Home Study*	–	–	–	–	–	–	–
MSAD Study*	–	–	–	–	–	–	–
Rivastigmine							
Sramek, *et al.*, 1996[44]	4/5	Not stated	N/A	N/A	N/A	N/A	N/A
Agid, *et al.*, 1998[45]	4/5	OC	CGIC (+)	MMSE (ns)	PDS (+)	N/A	FOME (+) NOSGP (ns) BVR (ns)
Corey-Bloom, *et al.*, 1998[46]	5/5	ITT	CIBIC-plus (+) GDS (+)	ADAS-cog (+) MMSE (ns)	N/A	N/A	N/A
Forette, *et al.*, 1999[47]	2/5	OC	CIBIC-plus (+)	ADAS-cog (ns)	N/A	N/A	NOSGP (ns)
Rosler, *et al.*, 1999[48]	5/5	ITT	CIBIC-plus (+) GDS (+)	ADAS-cog (ns) MMSE (+)	PDS (ns)	N/A	N/A
Novartis B304*	–	–	–	–	–	–	–
Novartis B351*	–	–	–	–	–	–	–
Galantamine							
Wilcock, *et al.*, 1997[49]	1/5	ITT	N/A	ADAS-cog (+)	N/A	N/A	N/A
Tariot, *et al.*, 2000[50]	5/5	LOCF	CIBIC-plus (+)	ADAS-cog (+)	ADL (+)	NPI (+)	N/A
Raskind, *et al.*, 2000[51]	5/5	LOCF	CIBIC-plus (+)	ADAS-cog (+)	ADL (ns)	N/A	N/A
Wilcock, *et al.**	–	–	–	–	–	–	–
Rockwood, *et al.**	–	–	–	–	–	–	–
Wilkinson, *et al.**	–	–	–	–	–	–	–

+ = significant beneficial effect; – = significant negative effect; ns = no significant effect

BVR, Benton Visual Retention; FOME, Fuld Object Memory Evaluation; GDS, Global Deterioration Scale; IDDD, Interview for Deterioration in Daily living in Dementia; LOCF, last observation carried forward; NOSGP, Nurse Observation Scale for Geriatric Patients

** CIC data, omitted*

related QoL in people with dementia: the development of a new instrument responsive to change and an evaluation of current methodology' is being undertaken.

- Outcomes of behaviour and mood were rarely included in RCTs.* For galantamine one published study showed significant benefit.* There were no published studies of donepezil or rivastigmine that included such measures.
- By focusing on donepezil, rivastigmine and galantamine, this review excluded a number of other interventions. For example, metrifonate (an old drug) has been shown to have a statistically significant effect in delaying progression as assessed on the ADAS-cog.[36] All trials reported a statistically significant effect of treatment on ADAS-cog scores at the end of the double-blind phase. The magnitude of the difference varied across the trials. The magnitude of the effects on the ADAS-cog was maximal at the highest dose whether the study was of 12 weeks' or 26 weeks' duration. All of the trials found a significant treatment effect on global function as measured by the CIBIC-plus. The treatment/placebo differences between baseline and the end of the double-blind phase were very similar across trials.
- There are continuing developments in the different treatments for people with AD. Appendix 14 lists drugs for AD that are undergoing clinical trials. With published and unpublished evidence on the clinical effectiveness of donepezil, galantamine, rivastigmine and the other developing interventions continuing to emerge (see appendix 15), it will be important to update this rapid systematic review within 18 months.
- Patients included in the studies had been diagnosed using recognised criteria (including DSM-III-R and NINCDS) and were thought to have mild to moderate AD. As noted by Birks and Melzer,[35] patients with co-existing illness or concurrent treatment were often excluded from trials, providing a healthier patient population than might be seen in practice.
- Although there are numerous measurement scales for assessing disease progression through a worsening in the domains of cognition, functional ability and behaviour and mood, the outcome measures used in studies to date have concentrated on ADAS-cog and CIBIC-plus. Although the scales used have been shown to be reliable and valid, all scales are proxy measures that may not reflect outcomes important to people with dementia or their carers. There is limited assessment of their responsiveness to change and what this means to patients and carers. Any conclusion drawn concerning the clinical effectiveness of these drugs should be limited to the outcomes assessed.
- A seven-point change in the ADAS-cog may be regarded as clinically significant,[72] but this was not achieved in the trials, although the percentage of patients with a four-point change is reported. Average results conceal a range of outcomes, with some patients doing much better, but it should be noted that some patients in the placebo groups also showed good improvement.
- In studies using QoL measures assessed by patients or carers there was limited evidence of effect, or in some instances a deterioration in QoL. In these studies, it was suggested that patients and carers might be unreliable in assessing the effect of the intervention. This may be accurate, although it could be that the drug slows progression but maintains the patient in a condition that may be distressing to the patient and the carer.
- Adverse effects reported in the trials appeared to be mild and transient. They did not include the adverse effects noted by the Committee on Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products, which included depression, tremor, angina pectoris and gastrointestinal haemorrhage for rivastigmine. In addition, the CPMP report noted that there were 57 deaths in the rivastigmine trials (52 patients on active treatment, five patients on placebo), although it indicated that this did not suggest an increased mortality rate.
- Studies included in this review tended to report results as observed case (OC) and LOCF, with limited reporting of results using ITT analysis. Results presented using OC or LOCF are prone to bias when there are high numbers of drop-outs. OC excludes patients not reaching the study end-point, whereas LOCF replaces missing patient values at study end-point with the last observation available. It is conceivable that attrition was non-random with more patients dropping out of the intervention rather than the placebo groups. Patients who withdraw from studies are more likely to be at a more severe stage of AD. Hence, the results presented in OC and LOCF analyses

* Discussion of unpublished studies (CIC data) omitted

may be more favourable for the intervention group and misleading compared with the more conservative ITT analyses. Where available we have reported results as ITT analyses, but in many instances only LOCF analyses were available and caution should be taken in interpreting these results.

Implications for research

In undertaking the rapid review of drugs in AD, certain implications for research have become evident. These include the following.

- The studies in the review used a range of outcome measures and there is concern about their adequacy, in particular their clinical meaning and relevance to patients and carers. The results of the AD2000 study may clarify the correlation between surrogate measures of disease progression such as cognition (e.g. ADAS-cog and MMSE) and clinically relevant outcomes such as behaviour, function and carer well-being. AD2000 is still recruiting and should reach its target by the end of 2001, with publication of the main results in 2002. The five main questions the study aims to answer are:
  1. does donepezil produce clinical, social, or economically worthwhile benefits for AD patients?
  2. if so, how long do benefits last?
  3. is 10 mg donepezil more effective than 5 mg?
  4. can presentation characteristics or response to 12 weeks' treatment predict which patients may benefit?
  5. does aspirin have an effect on the progress of AD, on its own or together with donepezil?
- Typically, interventions were administered for limited periods within the studies – usually for 12 to 30 weeks. There is little good quality published evidence of the long-term effects of administering AChEIs.* As the clinical progression of AD varies between individuals and may continue beyond 5 years, the long-term effects of treatment with these drugs remain unknown. However since AChEIs do not affect the underlying disease process, their effect will inevitably be temporary – over time there will be less of the acetylcholine transmitter to preserve.
- Further research is required on monitoring of patients and any benefit due to treatment, to identify those patients likely to benefit from treatment, and on the development of protocols for withdrawal from treatment if there is no response, or when any observed response fades.
- There is a need to develop a QoL measurement for patient and carers; in particular research is needed on how to measure the value of delaying symptoms.
- There is also a need to compare the benefits achieved from drug therapy with outcomes from other key interventions such as rehabilitation and home support.

* Discussion of unpublished studies (CIC data) omitted

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Appendix 1

Memory clinic costs

Outpatient costs for a memory clinics

	Total salary (£)	Sessions per year	Cost per session (£)
Staff costs			
Consultant geriatrician	58,000	484	119.83
Consultant psychiatrist	58,000	484	119.83
Senior clinical psychologist	45,000	450	100.00
Clinic nurse – f grade	18,597	450	41.33
Counselling nurse – f grade	18,597	450	41.33
Total...	–	–	*422.32*
Overheads			
Hotel services	–	–	21
Property costs	–	–	21
Administration/supplies	–	–	64
Charges	–	–	43
Total...		–	*149*
Total cost per session	**–**	**–**	**571**
Cost per patient attendance	**–**	**–**	**95**
Figures are based on a clinic held at Ninewells Teaching Hospital, Dundee			

Note the following

1. Costs are for 1995/96
2. Assumes staff carry out one memory clinic session per week
3. Six patients seen per session
4. Assume 44 working weeks per year for medical staff (consultant geriatrician, consultant psychiatrist), and 45 working weeks per year for non-medical staff
5. Staff numbers were obtained from Professor McMurdo, Dundee University
6. Staff costs do include National Insurance and Superannuation
7. Hotel services etc. costs were provided by A. McCulloch DHC finance and are derived from figures produced by DTH finance
8. The additional cost of a CT scan, if required, is £142.96 using a fully depreciated scanner. This figure is based on DTH, and will vary widely amongst hospitals depending on type of scanner, age and depreciation, throughput, etc.

Source: SHPIC Costing Unit 1997

We thank Professor McMurdo and colleagues for assistance

Comparison of costs of a memory clinic

Hospital	First attendance (£)	Follow-up visit (£)	Cost per attendance (£)	Cost per case (£)
Ninewells, Dundee	N/A	N/A	95	N/A
Frenchay, Bristol	154	78	N/A	N/A
Addenbrooke's, Cambridge	N/A	N/A	N/A	227
Princess Alexandra, Harlow	108	82	N/A	N/A
Leicester	N/A	N/A	112	N/A
Whittington, London	N/A	N/A	115	N/A
Nether Edge, Sheffield	160	53	73	N/A
Cardiff Royal Infirmary	129	78	N/A	167
Hammersmith Trust, London	149	103	N/A	N/A

N/A, not available

Note the following

1. Figures were gathered from a telephone survey of outpatient memory clinics in the UK
2. Costs were sourced from appropriate contracts departments
3. There is obviously much variation in the method of costing for each clinic

A breakdown of specific costs was not possible from the data gathered. Thus, the costs should be interpreted loosely, and are therefore presented as a very general comparison

Appendix 2

Services used by people with AD

Service category	Service provider
Screening (over 75 years assessment) and early recognition	Primary care team
Assessment and treatment, including non-pharmacological dementia therapies (e.g. reality orientation, cognitive stimulation, validation therapy)	GP Day hospital Psychogeriatricians Liaison psychiatry Hospital inpatient and outpatient services Community resource teams Professions allied to medicine
Information counselling	Support groups, Alzheimer's Society Community psychiatric nurses Health visitor District nurse GP Hospital services (including day hospitals)
Community support	Meals on wheels Bathing/dressing Home help/care assistants Transport
Respite care	Day hospital Day care Holiday admissions Sitter services Family break schemes
Financial help	Cash payments Tax allowances Attendance allowance Invalid care allowance
Long-term residential care	Part III homes Warden-supervised accommodation Private residential homes Nursing homes Long-stay NHS wards

Appendix 3

Rapid and systematic review methods from the research protocol

Research question

- To undertake a rapid and systematic review of the clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease.

Clarification of research question and scope

- The aim of the review is to provide a rapid and systematic review of the effectiveness and cost effectiveness of the symptomatic treatments of donepezil, rivastigmine and galantamine for people suffering from Alzheimer's disease.
- As donepezil and rivastigmine were launched during the last 4 years, and galantamine has not been licensed, it is unlikely that there will be any direct comparisons of these drugs. Hence the evidence will probably focus on placebo controlled trials or trials with a non-drug comparator.
- The review will be from an NHS focus (costs and benefits). Where the evidence suggests there might be important costs falling on carers or other non-NHS organisations or carer benefits, these will be noted.

Report methods

- The review will be undertaken as systematically as time allows following the general principles outlined in NHS CRD Report 4.
- It should be noted that the research protocol will be updated as the research programme progresses. Any changes in the protocol will be notified to the NCCHTA and agreed with 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 (SilverPlatter), Internet Grateful Med or PubMed, EMBASE, National Research Register, Science Citation Index, BIOSIS, EconLit, MRC Trials database, Early Warning System and Current Controlled Trials. These will be searched for the periods covered by the databases up until March 2000 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 submissions to the National Institute for Clinical Excellence (NICE). In addition, a list of trials from the industry, as a check on the completeness of ascertainment of our searches.

Inclusion and exclusion criteria

- Interventions include the three drugs for Alzheimer's disease of donepezil, rivastigmine and galantamine.
- Participants include those people diagnosed with Alzheimer's disease that meet the criteria for treatment with donepezil, rivastigmine and galantamine.
- 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.
- Specific outcome measures will include activities of daily living, ADAS-cog, MMSE, clinical dementia ratings, CIBIC-plus, Global Deterioration Scale and Progressive Deterioration Scale.
- Outcomes will focus on those that are clinically relevant to patients with Alzheimer's disease and their carers.
- Economic evaluations of donepezil, rivastigmine and galantamine in people with Alzheimer's disease must include a comparator (or placebo) and both the costs and consequence (outcomes).
- Inclusion criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Data extraction strategy

- 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) six criteria, while RCTs will be judged using Jadad criteria (see appendices 1, 2, 3 and 4). Economic evaluations will be assessed using economic and decision analysis criteria developed from the JAMA user guides (see appendices 5 and 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

- The clinical effectiveness of donepezil, rivastigmine and galantamine will be synthesised through a narrative review with full tabulation of results of all included studies. Where thought appropriate a meta-analysis will be considered.

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

- Quality-of-life information to estimate Quality-Adjusted Life-Years (QALYs) will be obtained from the literature or consultation with experts.
- Costs will be sought from published sources (e.g. BNF or published studies) and where appropriate and available local NHS costs. Published studies will only include those with 'UK' costs as resource use varies internationally and currency conversions can markedly affect the overall costs.
- Where appropriate, cost/QALY will be estimated by combining effectiveness information from the trials and quality of life information (as above). Sensitivity analysis will be performed to determine how robust estimates are to the assumptions made.

Appendix 4

Sources of information, including databases searched and search terms

Databases searched	Issue or dates
The Cochrane Library (Systematic Reviews Database and Controlled Trials Register)	2000 Issue 1
MEDLINE (SilverPlatter)	1966–July 2000
NHS CRD, University of York: Database of Abstracts of Reviews of Effectiveness	To July 2000
NHS CRD, University of York: NHS Economic Evaluation Database	To April 2000
PubMed	To July 2000
EMBASE	1980–July 2000
National Research Register	2000 Issue 1
Science Citation Index	To July 2000
BIOSIS	To July 2000
EconLit	1969–March 2000
MRC Trials database	To July 2000
Early Warning System	To July 2000
Current Controlled Trials	To July 2000
Index of Scientific and Technical Proceedings	To July 2000
TOXLINE	To July 2000
GEARS (Getting Easier Access to Reviews; includes Drug and Therapeutics Bulletin, Effective Healthcare Bulletin, Effectiveness Matters, Bandolier)	2000 Version 1

Search terms used

donepezil
aricept
"e 2020"
memac
rivastigmine
exelon
"ena 713"
"sdz 212 713"
prometax
galantamine
galanthamine
jilkon
lycoremin*
nivalin*
gp37267
"gp 37267"
randomized controlled trial in pt
random*
blind* or mask*
placebo
explode "Dementia"/ all subheadings
alzheimer* or dementia
systematic near review
overview
meta-analys*
meta analys*
metaanalys*
integrative near review

Search strategy to identify economic evaluations

cost minimi?ation cost effective* analys* cost utility quality adjusted life year* or qaly* cost benefit analy* economic evaluation	NOT	pt = letter or pt = editorial or pt = news (for MEDLINE) dt = letter or dt = editorial (for EMBASE)	AND	"Alzheimer-Disease"/ all subheadings alzheimer*
alzheimer in NHS Economic Evaluation Database and EconLit*				

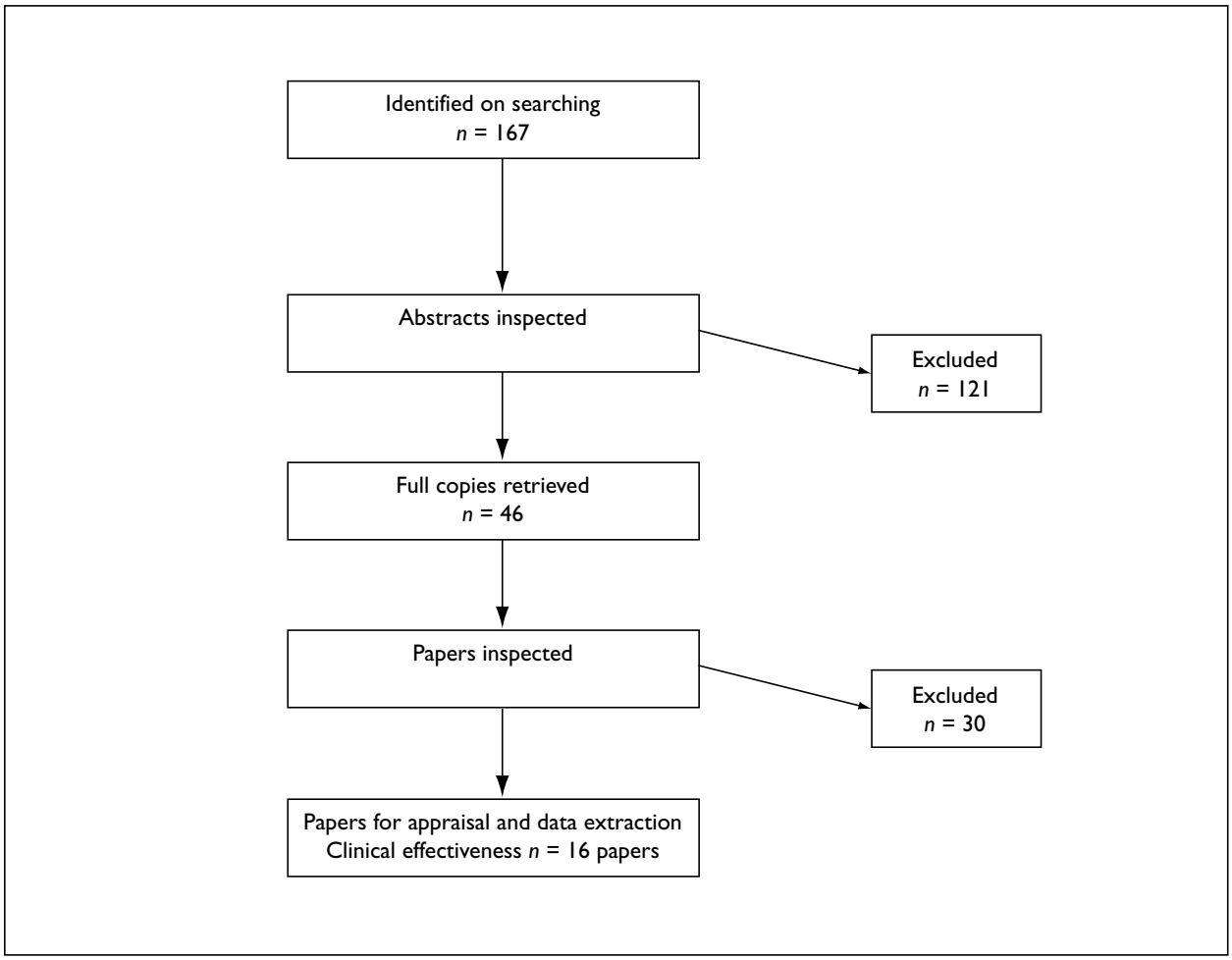

FIGURE 2 *Flowchart of identification and inclusion of studies (RCTs and systematic reviews) from initial search for the rapid systematic review of donepezil, rivastigmine and galantamine for AD*

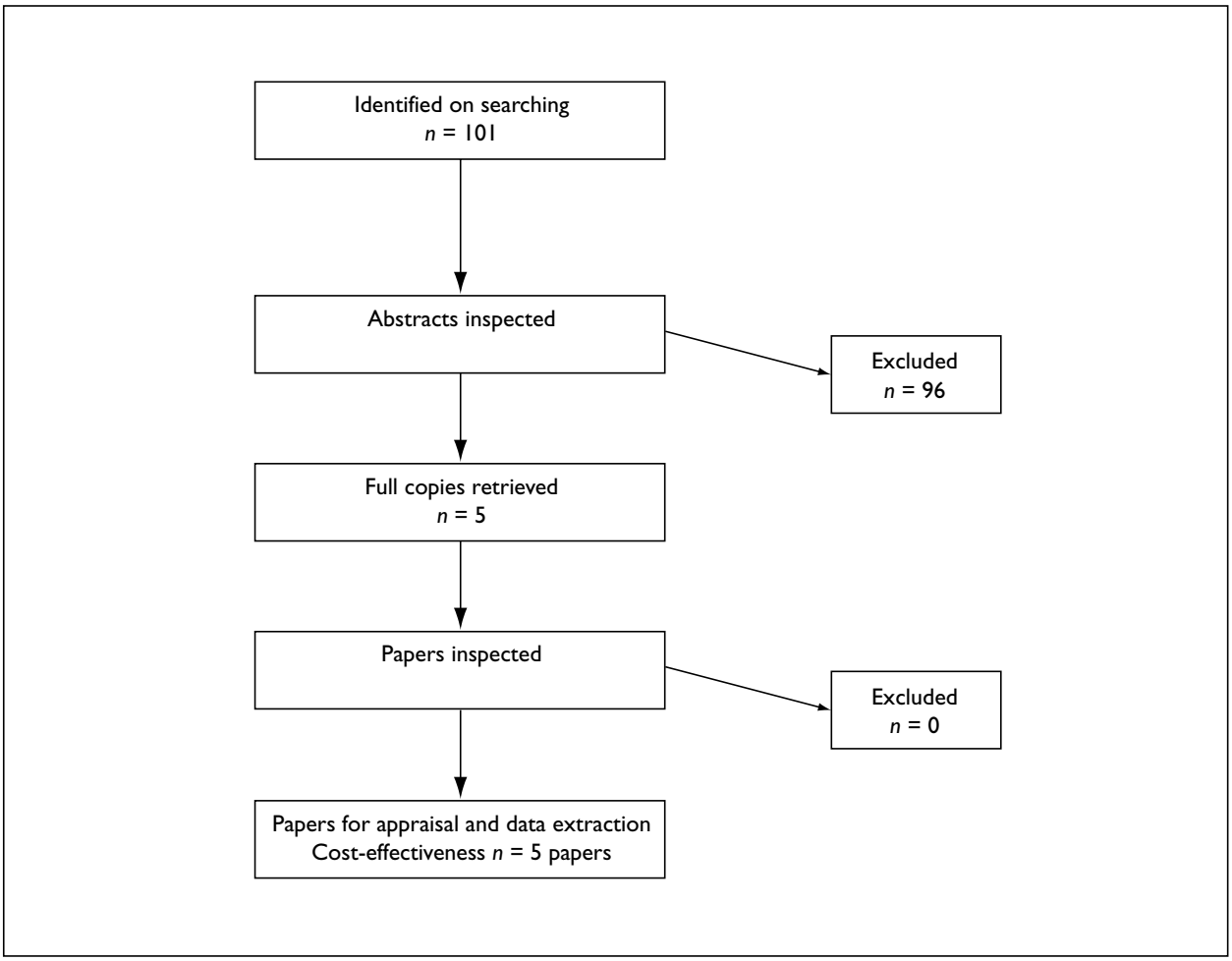

FIGURE 3 *Flowchart of identification and inclusion of studies of costs, economic evaluations, and studies of QoL (economics) for the rapid systematic review of donepezil, rivastigmine and galantamine for AD*

Appendix 5

Instrument to measure the likelihood of bias in RCTs (Jadad quality score)[30]

Questions to assess the likelihood of bias

- Was the study described as randomised (this includes the use of the words such as randomly, random and randomisation)?
- Was the study described as double-blind?
- Was there a description of withdrawals and drop-outs?

Scoring the items

Give a score of 1 point for each 'yes' and a score of 0 points for each 'no' There are no in-between marks.

Give 1 additional point if:

- for question 1, the method to generate the sequence of randomisation was described and it was appropriate (table of random numbers, computer-generated, etc.)

and/or

- if for question 2 the method of double-blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.).

Deduct 1 point if:

- for question 1, the method to generate the sequence of randomisation was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)

and/or

- for question 2, the study was described as double-blind but the method of blinding was inappropriate (e.g. comparison of tablet vs injection with no double dummy).

Guidelines for assessment

Randomisation

A method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

Double blinding

A study must be regarded as double-blind if the word 'double-blind' is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.

Withdrawals and drop-outs

Participants who were included in the study but did not complete the observation period or were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

Appendix 6

Quality assessment scales for systematic reviews[31]

Criteria for assessing good quality systematic reviews

Systematic reviews will be examined to determine how many of the following criteria for methodological quality they meet.

1. Does the review answer a well-defined question?
   A good review should focus on a well-defined question, making the objectives of the review easy to understand. The most important components in a review question include the target population, healthcare intervention and outcomes of interest.

2. Was a substantial effort made to search for all the relevant literature?

3. Are the inclusion/exclusion criteria reported and are they appropriate?
   Criteria for the inclusion of individual studies in a review have two major dimensions: relevance and validity. A relevant study should be useful to answer review questions in terms of patients, intervention and outcomes. The validity issue is related to the methodological standard of an individual study.

4. Is the validity of included studies adequately assessed?

5. Is sufficient detail of the individual studies presented?
   Details of the individual studies included in a review include study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate, effectiveness results and side-effects. The importance of the study details may differ for different review topics.

6. Have the primary studies been combined or summarised appropriately?

If at least four of the criteria are met the paper will be considered to be of good quality.

Appendix 7

Main outcome measurement scales used in trials of treatments for AD

Global outcome measures

Type	Construct measure and scoring	Critical appraisal
Clinical Global Impression of Change scale (CGIC); the global improvement index with interviewing of patients Clinician Interview-Based Impression of Change (CIBIC); and, with care-giver input (CIBIC-M or -Plus)	Overall improvement in patient health status assessed by clinician (-with care-giver) 1 (very much improved) to 7 (very much worse)	Poor to good test–retest and inter-rater reliability. Concurrent validity is poor to very good. Results may arise from fact that groups providing global assessments do not base their ratings on the same domains. Physicians take clinical psychopathology as the basis of determining global improvement; nurses believe the amount of work needed to care for patients is important. This instrument also includes care-giver opinion; results may differ depending on whether the rater interviews the patient or care-giver first. Amelioration of CGICs is needed before they are accepted as suitable outcome measures
Clinical Dementia Rating (CDR)	Cognitive impairment in memory, orientation, judgement/problem-solving, community affairs, home/hobbies, and personal care 0 = none, 0.5 = questionable, 1 = mild, 2 = moderate, 3 = severe	Provides physicians with a global rating that encompasses a broad range of patient characteristics and can be used by neurologists, psychiatrists, and psychologists and it focuses on cognition, not on items that may be related to other medical, emotional or social conditions Good inter-rater reliability and fair to good concurrent validity. Although no work has been done on test–retest reliability, nothing so far suggests that researchers should avoid this scale when trying to stage AD. The CDR can be used as an eligibility criterion for trial participation or as an outcome measure
Global Deterioration Scale (GDS)	Progressive stages of cognitive impairment 1 (no cognitive decline) to 7 (very severe cognitive decline)	Most frequently used but ratings can mis-state the severity of a patient's condition. Problems might arise when the GDS is used as an inclusion criterion for participation in an RCT. The ability to enrol desired patients could be threatened if the GDS misidentifies the stages of dementia The GDS should not be used to stage dementia in AD drug trials
Gottfries–Bräne–Steen (GBS)	Motor function, intellectual function, emotional function and symptoms common to demented patients 0 (normal function or absence of symptoms) to 6 (maximal disturbance or presence of symptoms)	Psychometric properties range from fair to good. Scale is useful mean of quantifying dementia in drug trials. GBS should not be used as a diagnostic tool
Mini-Mental State Examination (MMSE)	See cognitive outcome measurement scales	–

Cognitive outcome measurement scales

Type	Construct measure and scoring	Critical appraisal
Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog)	Orientation, memory, language and praxis 0–70, with higher scores indicating greater impairment	Limited in its ability to detect change at one end or the other of the severity continuum. For many subtests, detection of improvement appears to be possible only for a restricted range of severity levels Limitations should be considered when used as a drug efficacy measure. The rate of decline of AD using ADAS-cog suggests that the decline is not a constant but is dependent on the stage of the disease
Mini-Mental State Examination (MMSE)	11 questions on orientation, memory, concentration, language and praxis Scale ranges from 0 to 30. Higher score indicates less impairment. A cut-off of 23 of less has been adopted for cognitive impairment. A second cut-off of 17 or less is sometimes used for severe cognitive impairment	Good reliability and validity for its original purpose of screening for dementia; short screening scales are not designed to measure more subtle aspects of cognition. Short scales such as the MMSE may indicate little or no change over time in subjects who would otherwise be shown to have declined substantially if another scale had been used to measure change in status. Not an ideal outcome measure for AD drug trials, especially if the expected benefits are not large

Functional and QoL outcome measurement scales

Type	Construct measure and scoring	Critical appraisal
Physical Self-Maintenance Scale (PSMS)	Measured through competence of 6 behaviours: toileting, feeding, dressing, grooming, locomotion and bathing. It can be completed by untrained staff based on information from patients, care-givers, friends etc. Each behavioural area is given a score of 1 or 0, with overall score ranging from 0 to 6. Using Guttman scaling, each scale point has 5 descriptive scale points	Brief assessment of activities of daily living. Theoretically well grounded, it has been proven useful for evaluation of institutionalised elderly people but has a ceiling effect for those living in the community. Testing of psychometric properties is incomplete
Instrumental Activities of Daily Living (IADL)	For women, the set of behaviour assessed includes telephoning, shopping, food preparation, housekeeping, laundering, use of transport, use of medicine and ability to handle money. For men, the areas of food preparation, housekeeping and laundering are excluded Each of the behavioural areas is given a score of 0 or 1, leading to an overall score that ranges from 0 to 8 for women and from 0 to 5 for men	The IADL is a very frequently used and often cited instrument for assessing the instrumental competence of elderly patients. The scale is well anchored from a theoretical point of view and the behaviours that are included are likely to be affected in the first stages of dementia
The Interview for Deterioration in Daily Living in Dementia (IDDD)	The IDDD measures functional disability in self-care (16 items such as washing, dressing and eating) and complex activities (17 items such as shopping, writing, and answering the telephone) Severity of impairment is rated on a 7-point scale, where 1–2 = no or slight impairment, 3–4 = mild impairment, 5–6 = moderate impairment, 7 = severe impairment, giving a total range score of 22–231	This scale appears to be appropriate to assess community-living patients with mild and moderate levels of dementia. It assesses a substantial proportion of complex activities likely to be affected during the first stages of the AD. The number of non-redundant items in the scale is viewed positively since it may increase the sensitivity of the tool. Empirical information on the testing of the IDDD and its measurement properties is seriously lacking
Unified Activities of Daily Living Form (Unified ADL)	All self-care and mobility variables commonly used to assess patient's functional status A 20-item scale was produced. The need for assistance is scored for every item, on a 10-point scale	–
Quality of Life Scale (QoL)	Social indicators encompassing working, leisure, eating, sleeping, social contact, earning, parenting, loving, environment and self-acceptance Items are assessed on a 6-point rating scale and assigned 0, 10, 20, 30, 40 or 50 points > 350 = fairly successful QoL; 250–349 = painful but adequate coping; 100–249 = persons are suffering a great deal and seek help; < 100 = institutionalised mental patients	The scale is in an early stage of development and data on reliability, validity and responsiveness to change are lacking

continued

Functional and QoL outcome measurement scales *contd*

Type	Construct measure and scoring	Critical appraisal
The Progressive Deterioration Scale (PDS)	PDS examines activities of daily living and instrumental activities of daily living. Examples are: extent to which a patient can leave the immediate neighbourhood, use of familiar household implements, involvement in family finances, budgeting Each question is scored by measuring the distance along the line on a scale from 0 to 100. A composite score is derived from averaging across the items for a maximal score of 100	This scale has been shown to be sensitive to three severity stages of dementia and to have good reliability and validity

Behaviour and mood outcome measurement scales

Type	Construct measure and scoring	Critical appraisal
Neuro-psychiatric Inventory (NPI)	Currently evaluates 12 items: delusions, hallucinations, dysphoria, anxiety, agitation, euphoria, apathy, irritability, disinhibition, aberrant motor behaviour, night-time behaviour and changes in appetite/eating behaviour. Psycho-metric properties were established on first 10 items. Total score for each domain is calculated by multiplying frequency rating by severity rating, adding domain scores to get a total score. Higher scores represent more problems. Maximum score is 12 per domain, with either 10 or 12 domains assessed	Content validity has been established, reliability and validity are satisfactory. Limitations included: poor description of appraisal period for behavioural symptoms; no justification for scoring system; and inter-rater reliability was poorly deserved

Appendix 8

Summary of evidence of effectiveness of donepezil in AD

Reference and design	Research question and search strategy	Inclusion and quality criteria
Birks, *et al*., 2000 *Study design*: published update of Cochrane systematic review (last published amendment August 2000) *NHS CRD score*: 6/6	*Aim*: to assess whether donepezil improves the well-being of patients with mild or moderate AD *Search strategy*: The Cochrane Dementia and Cognitive Improvement Group Register of Clinical Trials, including MEDLINE, PsycLIT, EMBASE, SIGLE, ISTP, INSIDE, ASLIB, Dissertation Abstracts, ADEAR, NRR, Current Controlled Trials, Glaxo-Wellcome Trials, Centerwatch Trials Database, were searched from inception to April/July 2000 using the key words 'donepezil', 'ARICEPT', and 'E202' Members of the Donepezil Study Group and Eisai Inc. were contacted	*Inclusion criteria* Study designs: unconfounded RCTs. Trials with inadequate methods of randomisation or concealment were excluded. Follow-up non-randomised studies were excluded from assessment of safety and efficacy Interventions: donepezil given at any dose administered for more than a day with parallel, concomitant placebo control group Population: patients diagnosed as having probable AD according to accepted criteria such as ICD-10, DSM, NINCDS-ADRDA. Studies using MMSE varied in their definition of mild to moderate, varying within the range of 5–26. Participants had mild to moderately severe AD, or were elderly patients in nursing homes or were from clinical practice. Exclusions were consistent across studies, including: evidence of insulin-dependent diabetes mellitus or other endocrine disorder, asthma, obstructive pulmonary disease or clinically significant uncontrolled gastrointestinal, hepatic or cardiovascular disease. Patients known to be hypersensitive to ChE inhibitors or who had taken tacrine or other investigational medicines within 1 month of baseline, or concomitant medications such as anticholinergics, anitrconvulsants, antidepressants and antipsychotics were excluded Setting: not specified Outcome measures: dependency; global impression; functional performance; behavioural disturbance; quality of life; cognitive function (measured by psychometric tests); effect on carer; death; acceptability of treatment as measured by withdrawal from trial; and safety as measured by the incidence of adverse effects (including side-effects) leading to withdrawal Quality criteria: as per Cochrane Collaboration guidelines in which randomisation is categorised as A (adequate), B (unclear) or C (inadequate), and Jadad score (blinding and loss before analysis) Application of methods: inclusion criteria were applied to titles and abstracts were assessed by one reviewer. Two reviewers independently reviewed selected trials for inclusion in the review. Quality criteria were applied by two reviewers. Data were extracted by one reviewer and cross checked.

continued

contd
Birks, *et al*., 2000

Results
Quantity and quality of studies: 8 RCTs were identified but only 7 reported sufficient detail to be included in the meta-analysis. Duration of studies and presentation of results was at 12 weeks or 24 weeks, with results for a longer term study at 52 weeks also reported. Donepezil doses were 5 and 10 mg/day. There was no formal quality assessment of the included studies presented, although only double-blind, placebo-controlled RCTs were included. It was noted that only 3 trials described allocation procedures

Overall: greater improvement in ADAS-cog and MMSE scores (assessed using WMD) for donepezil groups compared with placebo. Size of effect was dose-related with greater improvement in the donepezil 10 mg group

ADAS-cog (WMD): 12 weeks, 10 mg donepezil vs placebo (1 RCT, 303 patients) = –3.1 (95% CI, –4.2 to –1.9), heterogeneity $Z = 5.23$; 24 weeks 10 mg donepezil vs placebo (2 RCTs, 821 patients) = –2.9 (95% CI, –3.7 to –2.2), heterogeneity $Z = 7.6$; 12 weeks 5 mg donepezil vs placebo (3 RCTs, 488 patients) = –2.3 (95% CI, –3.2 to –1.5), heterogeneity $Z = 5.34$; 24 weeks 5 mg donepezil vs placebo (2 RCTs, 831 patients) = –1.9 (95% CI, –2.6 to –1.1) heterogeneity $Z = 4.89$

MMSE (WMD): 12 weeks 10 mg donepezil vs placebo (1 RCT, 306 patients) = –1.3 (95% CI, –1.8 to –0.9), heterogeneity $Z = 5.58$; 24 weeks 10 mg donepezil vs placebo (1 RCT, 304 patients) = –1.4 (95% CI, –2.1 to –0.7), heterogeneity $Z = 3.82$; 12 weeks 5 mg donepezil vs placebo (2 RCT, 382 patients) = –0.9 (95% CI, –1.5 to –0.4), heterogeneity $Z = 3.21$; 24 weeks 5 mg donepezil vs placebo (1 RCT, 307 patients) = –1.2 (95% CI, –1.9 to –0.5), heterogeneity $Z = 3.42$. At 52 weeks 10 mg/day donepezil vs placebo (1 RCT, 272 patients) = –1.7 (95% CI –2.6 to –0.8), heterogeneity $Z = 3.76$

CIBIC-plus: greater improvement in CIBIC-plus (Peto OR) for donepezil groups compared with placebo. 12 weeks, 10 mg donepezil vs placebo (1 RCT, 302 patients), OR = 0.4 (95% CI, 0.2 to 0.6), heterogeneity $Z = 3.89$; 24 weeks, 10 mg donepezil vs placebo (2 RCTs, 799 patients), OR = 0.5 (95% CI, 0.3 to 0.7), heterogeneity $Z = 4.15$; 12 weeks, 5 mg donepezil vs placebo (1 RCT, 303 patients) OR = 0.5 (95% CI, 0.3 to 0.8), heterogeneity $Z = 2.81$; 24 weeks, 5 mg donepezil vs placebo (2 RCTs, 812 patients), OR = 0.5 (95% CI, 0.4 to 0.7), heterogeneity $Z = 3.67$

CDR-SB: greater improvement in CDR-SB (WMD) for 5 mg and 10 mg donepezil compared with placebo at 24 weeks but not 12 weeks. 12 weeks, 10 mg donepezil vs placebo WMD (1 RCT, 304 patients) = –0.2 (95% CI, –0.5 to 0.1), heterogeneity $Z = 1.15$; 24 weeks, 10 mg donepezil vs placebo WMD (2 RCTs, 824 patients) = –0.5 (95% CI, –0.7 to –0.3), heterogeneity $Z = 4.49$; 12 weeks, 5 mg donepezil vs placebo WMD (3 RCTs, 487 patients) = –0.03 (95% CI, –0.3 to 0.2), heterogeneity $Z = 0.30$; 24 weeks, 5 mg donepezil vs placebo WMD (2 RCTs, 830 patients) = –0.4 (95% CI, –0.6 to –0.2). heterogeneity $Z = 3.80$

GBS: at 52 weeks 10 mg donepezil vs placebo (1 RCT, 276 patients) = –0.25 (95% CI –0.5 to 0.03), heterogeneity $Z = 1.73$

PDS: at 52 weeks 10 mg donepezil vs placebo (1 RCT, 276 patients) = –3.8 (95% CI –5.9 to –1.7), heterogeneity $Z = 3.55$

QoL: No evidence of difference in donepezil compared with placebo on patient-rated QoL Scale at 12 or 24 weeks. At 12 weeks, 10 mg donepezil vs placebo WMD (2 RCTs, 306 patients) = 8.30 (95% CI, 0.8 to 15.8), heterogeneity $Z = 2.2$; at 24 weeks, 10 mg donepezil vs placebo WMD (2 RCTs, 815 patients) = 2.8 (95% CI, –2.6 to 8.2), heterogeneity $Z = 1.0$; at 12 weeks, 5 mg donepezil vs placebo WMD (2 RCTs, 377 patients) = –3.1 (95% CI, –10.0 to 3.8), heterogeneity $Z = 0.87$; at 24 weeks, 5 mg donepezil vs placebo WMD (2 RCTs, 827 patients) –0.7 (95% CI, –6.0 to 4.6), heterogeneity $Z = 0.27$

Adverse reactions: nausea, vomiting and diarrhoea occurred more frequently in the 10 mg donepezil group than in the 5 mg group or placebo groups

Withdrawals:

There was an increased number of withdrawals from the 10 mg donepezil group compared with the placebo group but not for the 5 mg donepezil group compared with the placebo group. 12 weeks, 10 mg donepezil vs placebo (1 RCT, 311 patients), OR = 2.7 (95% CI, 1.4 to 5.2), heterogeneity Z = 2.94; 24 weeks, 10 mg donepezil vs placebo (3 RCTs, 1074 patients), OR = 1.4 (95% CI, 1.0 to 1.8), heterogeneity Z = 2.15; 52 weeks, 10 mg donepezil vs placebo (1 RCT, 286 patients), OR = 1.0 (95% CI, 0.6 to 1.7), heterogeneity Z = 0.08; 12 weeks, 5 mg donepezil vs placebo (3 RCTs, 513 patients), OR = 1.5 (95% CI, 0.9 to 2.7), heterogeneity Z = 1.46, 24 weeks 5 mg donepezil vs placebo (2 RCTs, 861 patients), OR = 1.0 (95% CI, 0.7 to 1.4), heterogeneity Z = 0.17

Withdrawals due to adverse events: 12 weeks, 10 mg donepezil vs placebo (3 RCTs, 513 patients), OR = 4.1 (95% CI, 1.6 to 10.4), heterogeneity $Z = 3.0$; 24 weeks, 10 mg donepezil vs placebo (2 RCTs, 861 patients), OR = 1.6 (95% CI, 1.2 to 2.3), heterogeneity $Z = 2.76$; 52 weeks, 10 mg donepezil vs placebo (1 RCT, 286 patients), OR = 1.1 (95% CI, 0.5 to 2.9), heterogeneity $Z = 0.27$. For 5 mg only, withdrawals at 12 weeks were significantly different from placebo (3 RCTs, 513 patients), OR = 2.3 (95% CI, 1.0 to 5.3), heterogeneity $Z = 2.02$; 24 weeks, 5 mg donepezil vs placebo (2 RCTs, 861 patients), OR = 0.9 (95% CI, 0.5 to 1.4), heterogeneity $Z = 0.52$

continued

contd
Birks, *et al.*, 2000

Methodological comments

- Search strategy: electronic databases, experts and industry were consulted for published and unpublished studies
- Participants: many patients with coexisting illness or concurrent treatment were omitted; patients were not likely to be representative of patients seen in clinical practice
- Inclusion/exclusion criteria: appropriately defined in terms of intervention, participants and outcomes assessed, as well as adequately applied. Use of similar strict inclusion criteria in all 3 included trials may limit general applicability
- Quality assessment: only double-blind, placebo-controlled RCTs were included, assessed using Cochrane methodology
- Method of synthesis: analysis was reported on an ITT basis with results input on an LOCF basis. Heterogeneity was assessed statistically but no comment was made on the heterogeneity. Meta-analysis using fixed effects models, WMDs, or Peto ORs (95% CI) was appropriate given the clinical similarity of participants and interventions and absence of heterogeneity on ADAS-cog and MMSE scores. Results from meta-analysis were reported as point estimates with 95% CI

General comments

- Selected patients with mild or moderate AD treated for periods of 12 or 24 weeks, donepezil 10 mg/day produced modest improvements in cognitive function and study clinicians rated global improvement more positively in treated patients. No improvements were present in patients' self-assessed quality of life, and data on many important outcomes were not available. The practical importance of these changes to patients and carers is unclear
- Several dimensions of outcome considered important in the review's protocol were not available from the primary studies
- No mention was made of baseline comparability of treatment groups or of methods to ensure double-blinding
- Concern over the question as to whether changes in cognitive tests are of practical relevance to patients or carers
- Omission of several dimensions of outcome considered important in the review's protocol
- Use of LOCF in the analysis is likely to favour reporting of greater improvement in the donepezil 10 mg/day group which has a higher drop-out rate than control
- Reports of agitation and aggressive behaviour in patients taking donepezil requires investigation
- Duration of trials was 24 weeks and longer term studies are required as are trials in populations more representative of the general population which utilise measures of dependency and effects on carers
- 7 out of 8 studies were supported by either Eisai Inc. or Pfizer Inc.

Quality assessment for systematic reviews (NHS CRD criteria)

Question	**Score**
1. Does the review answer a well-defined question?	1
2. Was a substantial effort made to search for all the relevant literature?	1
3. Are the inclusion/exclusion criteria reported and are they appropriate?	1
4. Is the validity of included studies adequately assessed?	1
5. Is sufficient detail of the individual studies presented?	1 (drop-outs reported as part of meta-analysis)
6. Have the primary studies been combined or summarised appropriately?	1

Reference and design	Research question and search strategy	Inclusion and quality criteria
Wolfson, *et al*., 2000[36] Canada *Study design*: systematic review *NHS CRD quality score*: 5/6	*Aim*: to assess and compare the evidence for the clinical efficacy of individual therapies for AD *Search strategy*: electronic databases included Applied Science and Technology, CINAHL, Core Biomedical Collection, Core Biomedical Collection III, HealthSTAR, MEDLINE, PsycINFO, Cochrane library and multi-media. Review articles were handsearched for references *Search Terms*: 'Rivastigmine', 'Donepezil', 'Alzheimer's Disease', 'Drug Therapy'	*Inclusion criteria* Study design: published trials that have the methodological integrity to provide the best evidence on donepezil, galanthamine and rivastigmine Intervention: donepezil, galantamine or rivastigmine versus placebo Population: patients with a diagnosis of probable AD using NINCDS/ADRDA diagnostic criteria Setting: not specified Outcome measures: not specified *a priori* but included ADAS-cog, CGIC, CIBIC-plus, CDR-SB and QoL as secondary outcome measures, MMSE as secondary cognitive performance outcome, IDDD, and PDS Quality criteria: methodological quality of the trials was assessed using the Jadad 6-item scale, with those ≥ 5 on Jadad scale being included Application of methods: it is unclear how inclusion criteria were applied. 3 reviewers independently assessed the trials for quality, with a consensus meeting to resolve any differences. It is unclear how the data were extracted

Results

Donepezil studies: 1 Phase II and 3 Phase III parallel, double-blind trials. The Phase II trial (1 mg/day, 3 mg/day, 5 mg/day and placebo) included 161 patients while the patient numbers in the Phase III trials (5 mg/day and 10 mg/day) ranged from 473 to 818 patients. Participants were considered similar in terms of demographic characteristics and disease severity. Analysis on ITT basis using the LOCF approach. Double-blind treatment duration ranged from 12 weeks to 24 weeks, with post-treatment placebo wash-out periods of 2 weeks, 3 weeks and 6 weeks

Quality assessment: the Jadad scores for the 4 trials on donepezil were all between 6 and 7

ADAS-cog: 5 mg donepezil versus placebo (4 RCTs of 12- or 24-weeks' duration) ranging from –1.5 ($p = 0.002$) to –3.2 ($p < 0.01$); 10 mg donepezil versus placebo (4 RCTs of 12- or 24-weeks' duration) ranging from –2.88 ($p < 0.001$) to –3.1 (95% CI, –4.22 to –1.92)

CGIC: in the Phase II, 12-week trial the percentage of patients in each treatment group who were rated as treatment success were reported: as 80% in the placebo group, 83% in the 1 mg/day group, 87% in the 3 mg/day group and 89% in the highest dose (5 mg/day) group. The differences between the 5 mg/day group and the placebo group was statistically significant ($p = 0.039$)

CIBIC-plus scale: treatment efficacy was defined as an improvement on the CIBIC-plus scale. One Phase III trial reported 14% of the placebo group, 21% of the 5 mg group and 25% of the 10 mg group had improved. This trial reported that a 5 mg:placebo difference of 0.3 ($p = 0.0326$) and a 10 mg:placebo difference of 0.4 ($p = 0.0009$) were observed. Another Phase III trial reported that 18 % of the placebo group, 32% of the 5 mg group, and 38% of the 10 mg group improved. In each case differences between treatment and placebo were statistically significant (p values not provided). Another Phase III trial defined treatment efficacy as no change or improvement on the CIBIC-plus scale and reported that 55% in the placebo group, 67% in the 5 mg/day group and 75% in the 10 mg/day group either remained the same or improved on the CIBIC-plus scale. This trial reported a treatment: placebo difference that was statistically significant for both the 5 mg (0.36, $p = 0.0047$) and the 10 mg/day group (0.44, $p < 0.0001$). Differing definitions make comparisons with the other trials difficult

MMSE score: in the 24-week trial the end of trial difference in changes in MMSE scores were 1.21 points ($p = 0.0007$) and 1.36 points ($p = 0.0002$) for the 5 mg/day and the 10 mg/day groups respectively. In the shorter trial (12 weeks) the difference were 0.6 points ($p = 0.004$) and 0.9 points ($p = 0.01$)

CDR-SB: 2 of the 4 donepezil trials found no apparent effect on the CDR-SB scores, while the two longer trials found evidence of a statistically significant improvement on the CDR-SB scores

QoL: only 1 trial found a statistically significant effect of donepezil on QoL, with the 10 mg/day group having a significant worsening compared with placebo

Adverse effects and drop-outs: donepezil was well tolerated and adverse events were reported to be mild to moderate in intensity. The prevalence of adverse events was high even in the placebo groups (65%, 69%, 76%). There were more reports of nausea, diarrhoea, vomiting and events involving the nervous system in the 10 mg treatment group. Other frequently reported (≥ 5%) adverse effects were: dizziness, common cold, headache, flushing, agitation, pain, constipation, nasal congestion, cough, gastric upset, insomnia, rhinitis

continued

contd
Wolfson, *et al*., 2000[36]

Methodological comments

- Search strategy: sources and limitations were adequately discussed
- Participants: characteristics of participants are discussed and effects on outcomes noted
- Inclusion/exclusion criteria: not explicitly stated *a priori* and method of application not discussed
- Quality assessment: Jadad 6-item score used, but limited discussion of scores for specific studies
- Method of synthesis: narrative synthesis, due to differences between the studies

General comments

- Trials on donepezil were supported by Eisai America Inc. and Eisai Co. Ltd, Tokyo
- Limited reporting on limitations and clinical relevance of the evidence
- All of the trials used the LOCF approach for drop-outs and this may have resulted in an overestimation of a treatment effect
- For the donepezil trials, overall between 77% and 88% of the patients completed the studies. There were more withdrawals in the high-dose groups in 2 of the studies. The high prevalence in 1 of these studies might be due to the forced titration from 5 mg/day to 10 mg/day over 1 week. This also compromised the validity of the efficacy results and the comparability of the studies

Quality assessment for systematic reviews (NHS CRD criteria)

Question	**Score**
1. Does the review answer a well-defined question?	1
2. Was a substantial effort made to search for all the relevant literature?	1
3. Are the inclusion/exclusion criteria reported and are they appropriate?	0
4. Is the validity of included studies adequately assessed?	1
5. Is sufficient detail of the individual studies presented?	1 (drop-outs reported)
6. Have the primary studies been combined or summarised appropriately?	1

Reference and design	Research question and search strategy	Inclusion and quality criteria
Livingston, *et al*., 2000[37] UK *Study design*: systematic review *NHS CRD quality score*: 4/6	Aim: to assess the clinical efficacy of cholinesterase inhibitors (donepezil, rivastigmine and tacrine) for people with AD Search strategy: electronic databases searched included MEDLINE (1966–1998), EMBASE (1994–1999) and PsycLIT (1974–1998) using keywords cholinesterase and placebo and dementia. No language restrictions	*Inclusion criteria* Study design: double-blind, randomised and placebo-controlled including > 10 patients and lasting > 1 day. Crossover and open-label phase studies were excluded Intervention: cholinesterase inhibitors Population: patients with a diagnosis of probable AD. Studies including other dementia were excluded Setting: not specified Outcome measures: not specified *a priori* but included ADAS-cog, CIBIC-plus, CIBI, MMSE, IDDD, and PDS Quality criteria: not stated Application of methods: not stated

Results (donepezil)

- ADAS-cog: no deterioration (5 mg), NNT 5 (95% CI, 4 to 9)
- ADAS-cog improvement ≥ 4 (5 mg), NNT 10 (95% CI, 5 to 180)
- ADAS-cog improvement ≥ 7 (5 mg), NNT 15 (95% CI, –828 to 8) (Note: figures checked and recalculated to –13 (95% CI, –785 to –6), suggesting NNT should read –15)
- ADAS-cog: no deterioration (10 mg), NNT 5 (95% CI, 3 to 8)
- ADAS-cog improvement ≥ 4 (10 mg), NNT 4 (95% CI, 3 to 7)
- ADAS-cog improvement ≥ 7 (10 mg), NNT 6 (95% CI, 4 to 12)
- CIBIC-plus improvement ≥ 3 (5 mg), NNT 7 (95% CI, 5 to 16)
- CIBIC-plus improvement ≥ 5 (5 mg), NNT 9 (95% CI, 5 to 94)
- CIBIC-plus improvement ≥ 3 (10 mg), NNT 8 (95% CI, 5 to 19)
- CIBIC-plus improvement ≥ 5 (10 mg), NNT 5 (95% CI, 4 to 11)

Methodological comments

- Search strategy: sources and limitations were adequately discussed
- Participants: limited discussion of characteristics of participants or effects on outcomes noted
- Inclusion/exclusion criteria: adequately stated and although method of application not discussed
- Quality assessment: not stated
- Method of synthesis: narrative synthesis based on the calculation of NNTs

General comments

- Studies show small numbers of patients need to be treated to ameliorate cognitive and non-cognitive symptoms or postpone deterioration
- Low doses produce no improvement in some cognitive outcomes

Quality assessment for systematic reviews (NHS CRD criteria)

Question	Score
1. Does the review answer a well-defined question?	1
2. Was a substantial effort made to search for all the relevant literature?	1
3. Are the inclusion/exclusion criteria reported and are they appropriate?	1
4. Is the validity of included studies adequately assessed?	0
5. Is sufficient detail of the individual studies presented?	0
6. Have the primary studies been combined or summarised appropriately?	1

Reference and design	Intervention	Patients	Outcome measures
Rogers, *et al*., 1996[38] USA *Study type/design*: multicentre, double-blind, parallel-group, placebo-controlled RCT (dose ranging study) *Jadad score*: 4/5	*Treatment arms*: 1. Donepezil 1 mg daily; 2. Donepezil 3 mg daily; 3. Donepezil 5 mg daily; 4. Placebo *Length of treatment*: 12 weeks followed by 2 weeks' wash-out *Other interventions used*: allowed sympathomimeticamines and antihistamines (not 48 hours pre- or post-clinic visit)	*Total number*: 161 patients donepezil 1 mg daily, 42 patients donepezil 3 mg daily, 40 patients donepezil 5 mg daily, 39 patients placebo, 40 patients *Characteristics of target population*: both sexes, aged between 55 and 85 years with mild to moderately severe AD (DSM-III-R and NINCDS) diagnosed at least 1 year before entry plus CT/MRI supporting evidence in 6 months before entry; MMSE between 10 and 26 inclusive; CDR of 1 or 2; females to be surgically sterilised/> 2 years post-menopausal; either ambulatory or ambulatory-aided (walker/cane) with adequate vision and hearing to comply with testing *Exclusion criteria*: other psychiatric/neurological disorder; diabetes; obstructive pulmonary disease; oncological or haematological disease; vitamin B_{12}/folate disorder; active gastrointestinal, renal, hepatic, endocrine/cardiovascular disease; history of alcoholism/drug abuse/cholinesterase inhibitor sensitivity *Participants*: weight range 32.0 to 104.3 kg; 96% Caucasian; 40% male. Body weight and height varied significantly ($p = 0.03$) between groups *Setting*: not specified	Outcome measures assessed at screening, baseline, 1, 3, 6, 9, 12 and 14 weeks after entry *Primary outcomes*: ADAS-cog CGIC *Secondary outcomes*: ADL MMSE CDR-SB Patient QoL scores assessed by patient (QoL-P) or caregiver (QoL-C) for relationships, eating and sleeping, and social/leisure activity *Adverse events*: TESS *Monitoring included*: Plasma concentration of donepezil, AChE activity in red blood cells haematology, clinical chemistry, urinanalysis, vital signs Follow-up: 14 weeks

Results

Primary outcomes

Adjusted mean change in ADAS-cog from baseline to end-point (min/max): donepezil 1 mg vs placebo was –0.9 (–11.3/12.0) vs 0.7 (–7.0/14.5), $p = 0.105$; donepezil 3 mg vs placebo –1.4 (–12.0/11.0) vs 0.7 (–7.0/14.5), $p = 0.036$); donepezil 5 mg vs placebo –2.5 (–8.0/7.0) vs 0.7 (–7.0/14.5), $p < 0.002$. Dose trend was statistically significant ($p < 0.04$)

CGIC: most patients scored as unchanged. Analysis adjusted for centre differences. Classifying CGIC scores 1 to 4 as success and 5 to 7 as treatment failures gave success rates as follows: placebo 81%; donepezil 1 mg 83%; donepezil 3 mg 87%: donepezil 5 mg 89%. Statistically significant reduction in failed visits for donepezil 5 mg vs placebo (11% vs 20%; $p = 0.039$), which differed little from end-point

Secondary outcomes

Adjusted mean change in ADL from baseline to end-point (min/max): no statistically significant difference between donepezil 1 mg at 4.0 (–25/97), 3 mg at 0.6 (–21/30), 5 mg at –3.1 (–36/15) and placebo at 1.5 (–38/57) reported. Only the adjusted mean scores for the donepezil 5 mg group improved relative to baseline

MMSE: no statistically significance between donepezil and placebo reported. Adjusted mean change from baseline reported as placebo 1.2; donepezil 1 mg 0.6; donepezil 3 mg 0.9: donepezil 5 mg 2.0

CDR-SB: no statistically significant changes from baseline to end-point (min/max) were found between donepezil 1 mg at 0.18 (–2.0/5.0), 3 mg at 0.23 (–3.0/6.0), 5 mg at –0.11 (–2.0/3.0) and placebo at 0.1 (–2.0/3.0)

QoL: no statistical significance between donepezil and placebo reported. A ceiling effect appeared present with both QoL measures

QoL-P: extensive inter- and intra-patient variability. Adjusted mean change from baseline (min/max) was not significant placebo –1.3 (–74/78); donepezil 1 mg 0.7 (–90/60); donepezil 3 mg 2.6 (–90/100); donepezil 5 mg 8.8 (–143/110). Significant dose trend ($p = 0.0369$)

QoL-C: marked inter-subject variability. Adjusted mean change from baseline was not significant: placebo 3.7 (–50/140); donepezil 1 mg –5.3 (–120/74); donepezil 3 mg 0.0 (–70/97); donepezil 5 mg 0.3 (–120/124)

Adverse events

Incidence of TESS in all donepezil groups (64% to 68%) was comparable to placebo (65%). Most frequent adverse reactions at 5 mg donepezil compared to placebo were as follows: nausea/vomiting (10% vs 5%); diarrhoea (10% vs 3%); dizziness (8% vs 10%), gastric upset (8% vs 5%) and constipation (8% vs 3%). Most TESS were of mild to moderate intensity. No clinically significant effect of donepezil was noted on vital signs, haematology or clinical biochemistry

continued

contd
Rogers, *et al.*, 1996[38]

Methodological comments
- Allocation to treatment groups: random, method not stated
- Comparability of treatment groups: considered comparable, although there were significant differences in height and weight
- Blinding: double-blind, using comparable dummy tablets
- Method of data analysis: analysis was ITT (included all randomised patients, received at least one dose of study drug, with at least one post-baseline data point). Conclusions based on combined results at each patient's last assessment. ANCOVA conducted to detect differences and pairwise comparisons conducted using Fisher's 2-tailed least significant difference procedure. Results reported at 'end-point' at each patient's last assessment during double-blind therapy
- Sample size/statistical power: sample size of 40 patients per group were estimated to achieve 80% power ($p \leq 0.05$) of detecting a 2.5-point improvement in the ADAS-cog score for donepezil compared to placebo
- Attrition/drop-out: drop-outs were reported by treatment group and with reasons

General comments
- Inclusion and exclusion criteria were clearly defined though the use of strict inclusion criteria may limit the generalisibility of the results
- The study was of short duration (12 weeks of active treatment and 2 weeks of wash-out). The regimen used for placebo treatment was comparable to the active treatment regimen
- Outcome measures were appropriate though it is not clear whether the quality of life scores were validated for use in this group
- Adverse reactions were reported by treatment group
- There was no assessment of inter-centre variability (though some results were adjusted for this effect) and little assessment of inter-patient variability. It is not clear whether the classification of CGIC scores 5 to 7 as treatment failures is supported by evidence and is justified clinically
- Supported by Eisai America Inc.

Quality assessment for systematic reviews (NHS CRD criteria)

Question	**Score**
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 1 (comparable dummy tablets)
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Total withdrawals 20 (12.4%): donepezil 1 mg daily, 19% donepezil 3 mg daily, 5% donepezil 5 mg daily, 12.8% placebo, 12.5%

TESS, treatment-emergent signs and symptoms

Reference and design	Intervention	Patients	Outcome measures
Rogers, *et al*., 1998[39] USA *Study type/design*: multicentre, double-blind RCT *Jadad score*: 5/5	*Treatment arms*: 1. Donepezil 5 mg/day 2. Donepezil 10 mg/day 3. Placebo *Length of treatment*: 24 weeks followed by 6 weeks, single-blind wash-out *Other interventions used*: not stated	*Number of patients*: Total: 473 (20 sites) 1. Donepezil 5 mg: 154 2. Donepezil 10 mg: 157 3. Placebo: 162 *Characteristics of target population*: aged ≥ 50 years, uncomplicated mild to moderate AD diagnosed using both DSM-III-R categories 290.00 or 290.10 and NINCDS-ADRDA, no clinical/other evidence of cause other than AD for dementia; MMSE scores between 10 and 26, CDR scores of 1 or 2, reliable care-giver *Exclusion criteria*: insulin-dependent diabetes, other endocrine disorder, asthma, obstructive pulmonary disease, clinically significant uncontrolled gastrointestinal, hepatic, or cardiovascular disease, hypersensitive to ChE inhibitors or taken tacrine and/or other investigational drugs within 1 month of baseline. Concomitant medications prohibited were anticholinergics, anticonvulsants, antidepressants, and anti-psychotics. Drugs with CNS activity either prohibited or restricted *Participants*: mean age 72.6, 72.9, 74.6 years in placebo, donepezil 5 mg and donepezil 10 mg groups, respectively; age range 51 to 94 years; 95% white; 38% male; baseline MMSE mean 19.2 (placebo), 19.0 (5 mg), 18.9 (10 mg); baseline CDR score 1.0 (75%), score 2.0 (25%). Age difference between placebo and donepezil 10 mg was significant ($p = 0.003$) *Setting*: not specified	Outcome measures assessed at baseline, 6, 12, 18, 24 and 30 weeks *Primary outcomes*: ADAS-cog CIBIC-plus *Secondary outcomes*: MMSE CDR-SB Patient-rated QoL *Others*: donepezil concentrations inhibition of red blood cell AChE activity clinical laboratory tests adverse event monitoring through TESS Length of follow-up: 30 weeks

Results

ADAS-cog (based on 153/162 placebo; 152/154 donepezil 5 mg; 150/157 donepezil 10 mg): statistically significant improvement in scores for both donepezil groups compared with placebo at 12, 18 and 24 week visits. Differences in means at 24 weeks: donepezil 5 mg vs placebo = –2.49 points ($p < 0.0001$); donepezil 10 mg vs placebo = –2.88 points ($p < 0.0001$). Proportion with poorer ADAS score: placebo 42.3%; donepezil 5 mg 20.3%; donepezil 10 mg 18.9%. Improvement of ≥ 4 points compared with baseline: placebo, 26.8%; donepezil 5 mg, 37.8%; donepezil 10 mg, 53.5%. Improvement of ≥ 7 compared with baseline: placebo, 7.8%; donepezil 5 mg, 15.4%; donepezil 10 mg, 25.2%

Change from baseline compared with placebo: 12 weeks, 5 mg $p = 0.0007$; 10 mg $p < 0.0001$; 18 weeks 5 mg $p = 0.0012$; 10 mg, $p < 0.0001$; 24 weeks, 5 mg $p < 0.0001$; 10 mg $p < 0.0001$

Dose–response mean (SEM) ADAS-cog change from baseline: placebo = 1.82 (± 0.49); 5 mg/day = –0.67 (± 0.51); 10 mg/day = –1.06 (± 0.51)

CIBIC-plus (based on 152/162 placebo; 149/154 donepezil 5 mg; 149/157 donepezil 10 mg): statistically significant improvement in scores for both donepezil groups compared with placebo from week 12 onwards. Differences in means at 24 weeks: donepezil 5 mg vs placebo = 0.36 points ($p = 0.0047$); donepezil 10 mg vs placebo = 0.44 points ($p < 0.0001$). Proportion improved (CIBIC ≤ 3): placebo, 11%; donepezil 5 mg, 26%; donepezil 10 mg, 25%

Change from baseline compared with placebo: 12 weeks, 5 mg $p = 0.0157$; 10 mg $p = 0.009$; 18 weeks, 5 mg $p = 0.0244$; 10 mg $p = 0.0002$; 24 weeks, 5 mg $p = 0.0047$; 10 mg $p < 0.0001$

Dose–response mean (SEM) CIBIC-plus change from baseline: placebo = 4.51 (± 0.08); 5 mg/day = 4.15 (± 0.09); 10 mg/day = 4.07 (± 0.07)

continued

contd
Rogers, *et al.*, 1998[39]

***Results* contd**
MMSE (based on 154/162 placebo; 153/154 donepezil 5 mg; 150/157 donepezil 10 mg): from week 12 onwards statistically significant improvement in scores for donepezil groups compared with placebo. Donepezil 5 mg vs placebo = 1.21 (p = 0.0007); donepezil 10 mg vs placebo = 1.36 (p = 0.0002)

Change from baseline compared with placebo: 12 weeks, 5 mg p = 0.0157; 10 mg p = 0.009; 18 weeks, 5 mg p = 0.00244; 10 mg, p = 0.0002; 24 weeks, 5 mg p = 0.0047; 10 mg $p < 0.0001$

Dose–response mean (SEM) MMSE change from baseline: placebo = –0.97 (± 0.28); 5 mg = 0.24 (± 0.29); 10 mg = 0.39 (± 0.29)

CDR-SB (based on 153/162 placebo; 154/154 donepezil 5 mg; 151/157 donepezil 10 mg): statistically significant improvement in scores for both donepezil groups compared with placebo from week 18 onwards. Difference in means at 24 weeks: donepezil 5 mg vs placebo = 0.59 (p = 0.0008); donepezil 10 mg vs placebo = 0.60 (p = 0.0007)

Patient-rated QoL: although improved from 12 weeks on, no significant differences in treatment effect. Only donepezil 5 mg group was significantly improved compared with baseline (p = 0.05) at week 24

Treatment wash-out: after 6 weeks' wash-out period on placebo, patient scores reverted to levels not statistically different from placebo for all outcome measures

CDR-SB change from baseline compared with placebo: 18 weeks, 5 mg/day p = 0.0105; 10 mg/day p = 0.0337; 24 weeks 5 mg/day p = 0.0007; 10 mg/day p = 0.0008

Dose–response mean CDR-SB change from baseline: placebo = 0.58 (± 0.14); 5 mg = –0.01 (± 0.14); 10 mg = –0.02 (± 0.14)

Adverse effects:
Not included in ADAS-cog analysis: placebo, 9%; donepezil 5 mg, 1%; donepezil 10 mg, 4%

Not completing assigned treatment: placebo, 20%; donepezil 5 mg, 15%; donepezil 10 mg, 32%

Withdrawals due to adverse events: placebo, 7%; donepezil 5 mg, 6%; donepezil 10 mg, 16%

Significantly more common in donepezil treated patients compared with placebo were the following TESS reported as placebo vs donepezil 5 mg vs donepezil 10 mg (based on all randomised patients): fatigue (2% vs 5% vs 8%), diarrhoea (7% vs 9% vs 17%), nausea (4% vs 4% vs 17%), vomiting (2% vs 3% vs 10%), muscle cramps (1% vs 6% vs 8%)

Treatment emergent biochemical/haematological abnormalities were similar among treatment groups

Methodological comments
- Allocation to treatment groups: random, using computer-generated allocation
- Comparability of treatment groups: considered comparable on demographic characteristics, with age being significantly different between placebo and donepezil 10 mg (p = 0.03)
- Blinding: double-blind, using comparable regimens
- Method of data-analysis: analysis was conducted on an ITT basis (included all those randomised, received at least one dose of study drug, provided complete baseline data, plus a minimum of one post-baseline point) though analysis conducted on fewer patients than number originally randomised. Conclusions based on last assessment (LOCF). Results were not presented consistently as point estimates of difference between active treatment and placebo with 95% CI. Assessment of efficacy contained factors for baseline score, treatment effect and centre effect, and treatment by centre interaction and random error
- Sample size/statistical power: sample size estimations were conducted to achieve 80% power of detecting a 0.27 point difference in mean CIBIC-plus score for each donepezil treatment group at 0.05 significance level
- Attrition/drop-out: % completing trial according to assigned treatment, and % discontinuing due to adverse reaction were given but reasons were not described

General comments
- Inclusion and exclusion criteria were clearly defined though the use of strict inclusion criteria may limit the generalisibility of the results
- Outcome measures were appropriate although it was not clear if the QoL measure had been validated for use in this group
- There was no indication of the extent of inter-centre variability
- Phase III study; 2 authors from Eisai Inc.

continued

contd
Rogers, *et al*., 1998[39]

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1 (computer-generated)
Was the study described as double-blind?	1 + 1 (comparable regimens)
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 20% placebo: 20% donepezil 5 mg: 15% donepezil 10 mg: 32%

Reference and design	Intervention	Patients	Outcome measures
Rogers, *et al*., 1998[40] USA *Study type/design*: multicentre double-blind, placebo-controlled, RCT (23 centres) *Jadad score*: 4/5 (See Friedhoff, *et al*., 1997)	*Treatment arms*: 1. Donepezil 5 mg/day 2. Donepezil 10 mg/day 3. Placebo *Length of treatment*: 12 weeks followed by 3 weeks single-blind wash-out *Other interventions used*: none stated	*Number of patients*: Total: 468 1. Donepezil 5 mg: 157 2. Donepezil 10 mg: 158 3. Placebo: 153 *Characteristics of target population*: age > 50 years with mild to moderate AD (DSM III-R); NINCDS; CT/MRI scan within 6 months of entry; MMSE scores 10 to 26; CDR rating of 1 or 2; either ambulatory or ambulatory-aided (walker/cane) with adequate vision and hearing to comply with testing *Exclusion criteria*: no additional diagnosis of delusions, delirium, depression, other psychiatric/neurological disorder; type 1 diabetes; obstructive pulmonary disease; asthma; haematological or oncological disease in last 2 years; vit B_{12}/ folate disorder; active gastrointestinal, renal, hepatic, endocrine/cardiovascular disease that was not controlled by diet; history of alcoholism/drug abuse/ cholinesterase inhibitor sensitivity/Hachinski ischaemia score of 5 or more. Hypnotics and cold preparations were allowed but not within 48–72 hours of clinic visit (90% of patients received such treatment) *Participants*: mean age 73.7 years (range 50 to 94 years); body weight ranged from 35.5 to 105.2 kg; 36% male; CDR 1% scored 0.5; 77% scored 1; 21% scored 2; MMSE: mean (SEM) per group for placebo 19.8 (0.35); 5 mg 19.39 (0.39); 10 mg 19.35 (0.40). Range 8 to 28 *Setting*: outpatient	Outcomes were assessed every 3 weeks to an end-point of 12 weeks *Primary outcomes*: ADAS-cog CIBIC-plus *Secondary outcomes*: MMSE CDRS-SB QoL assessed using 7-item patient-rated scale evaluating patients perceptions of relationships, eating and sleeping, and social and leisure activities. Items scored on analogue scale from 0 (worst) to 50 (best). Not been validated in patients with AD Adverse reactions Treatment compliance assessed. Considered compliant when 80% or more of required medication taken Length of follow-up: 15 weeks

Results

ADAS-cog: Least squares mean change in ADAS-cog from baseline: mean improvement score at end-point, adjusted for baseline severity was significantly greater for the 5 mg (–2.1; SEM 0.43; $p < 0.001$) and 10 mg (–2.7; SEM 0.43; $p \leq 0.001$) compared with placebo (0.4; SEM 0.43). Drug–placebo differences were 2.5 ADAS-cog for 5 mg and 3.1 ADAS-cog for 10 mg. Between drug differences were not significant ($p = 0.28$). Change in least square mean at 12 weeks adjusted for baseline covariate. Scores after a 3-week placebo wash-out period had begun to return to baseline levels. Change in least square mean (SEM) at week 15 (after wash-out): placebo = 1.5 (0.47); donepezil 5 mg = –0.7 (0.47); donepezil 10 mg = –1.6 (0.49)

CIBIC-plus: statistically significant improvement in both donepezil groups at week 12. Compared with placebo (4.2 ± 0.07) donepezil 5 mg had a mean score of 3.9 ($p = 0.003$) and donepezil 10 mg a mean score of 3.8 ($p = 0.008$) Improvements in mean CIBIC-plus score at end-point were significantly greater for the 5 mg group (3.9; SEM 0.08; $p = 0.003$) and 10 mg group (3.8; SEM 0.08; $p = 0.008$) compared with placebo (4.2; SEM 0.07). Drug–placebo differences were 0.3 for 5 mg and 0.4 for 10 mg. Percentage of patients demonstrating clinical improvement at end-point (CIBIC-plus score of 1, 2 or 3) were placebo 18%, 5 mg 32% and 10 mg 38%

MMSE: statistically significant improvements present in donepezil groups at end-point. Change in least square mean at 12 weeks adjusted for baseline covariate. Donepezil 5 mg vs placebo = 1.0 (95% CI, 0.33 to 1.65; SEM 0.25; $p < 0.004$); donepezil 10 mg vs placebo = 1.3 (95% CI, 0.65 to 1.97; SEM 0.25; $p < 0.001$). At week 15 (after 3 week wash-out) change in scores for both donepezil groups remained significantly improved. Change in least square mean (SEM) at week 15: placebo = –0.03 (0.27); donepezil 5 mg = 0.7 (0.27); donepezil 10 mg = 0.8 (0.28)

CDRS-SB: no statistically significant difference among treatment groups at any visit, with least squares mean change (SEM) in placebo of –0.14 (0.11), donepezil 5 mg of –0.10 (0.11) and donepezil 10 mg of –0.31 (0.11) ($p = 0.32$)

QoL: results were highly variable between and within patient groups. Patients receiving placebo showed an improvement in least squares mean change at end-point (4.0; SEM 2.7) as did patients on 5 mg (5.7; SEM 2.7) which was not significantly different from placebo ($p = 0.65$). Patients receiving 10 mg experienced a significant worsening compared with placebo (–4.3; SEM 2.7; $p = 0.02$)

continued

contd
Rogers, *et al*., 1998[40]

Adverse effects:
Rates of TESS were similar across treatment groups. Placebo = 69%; 5 mg = 68%; 10 mg = 78%. 92% of TESS were considered mild. The only adverse reactions that were significantly more common ($p < 0.001$) in the donepezil group were: nausea (placebo 8%; 5 mg 7%; 10 mg 22%); insomnia (placebo 5%; 5 mg 8%; 10 mg 18%); and diarrhoea (placebo 3%; 5 mg 6%; 10 mg 13%).
7 patients in the placebo group and 6 in each of the donepezil groups experienced serious adverse reactions. Included stomach ulcer with haemorrhage, syncope, transient ischaemic attack, nausea, aphasia, tremor and diaphoresis. 1 patient in placebo group died from renal failure. Donepezil-treated patients had significantly greater decreases in mean heart rate than placebo patients (2.65/min in 5 mg group; 2.26/min in 10 mg group; vs 0.09/min in placebo; $p < 0.03$). 2 patients in 5 mg group had notable ECG changes

Methodological comments
- Allocation to treatment groups: random, no details provided
- Comparison of treatment groups: patients were considered similar on demographic and baseline outcome measures of disease severity
- Blinding: double-blind, using comparable dummy placebo
- Method of data-analysis: reported as ITT with analysis end-point defined as the last assessment obtained for each patient prior to data cut-off point while on donepezil treatment. End-point considered as 12 weeks. Secondary analysis was conducted in evaluated patients (those completing 12 weeks with 80% compliance). Results were consistent between ITT and evaluated patients. For ADAS-cog, MMSE, CDRS-SB and QoL, ANOVA was used to compare treatment groups to baseline. Where differences occurred, Fisher 2-tailed least significant difference procedure was used. CIBIC-plus was analysed by Cochran–Mantel–Haenszel test
- Sample size/statistical power: *a priori* sample size estimates of 150 patients per group were calculated to detect a difference of 0.27 points in the mean CIBIC-plus scores between placebo and each active treatment group given a power of 80%, a $p = 0.05$ and a completion of 8%
- Attrition/drop-out: reported and taken into account in the analysis

General comments
- Inclusion and exclusion criteria were clearly defined though the use of strict inclusion criteria may limit the generalisibility of the results
- The study was of short duration (12 weeks of active treatment and 3 weeks of wash-out)
- Outcome measures apart from QoL were appropriate and the lack of validation of the instrument used to assess QoL was acknowledged
- Drop-outs were reported with reasons and by treatment groups
- Results were adjusted by treatment centre but there was no indication of the effect size of the centre or exploration of this effect
- Study supported by Eisai America Inc.

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 1 (comparable dummy placebo)
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 12% placebo: 7% donepezil 5 mg: 10% donepezil 10 mg: 18%

Reference and design	Intervention	Patients	Outcome measures
Burns, *et al.*, 1999[41] Multinational (82 sites in Australia, Belgium, Canada, France, Germany, Ireland, New Zealand, South Africa, UK) *Study type/design*: multinational, double-blind, parallel-group RCT *Jadad score*: 4/5	*Treatment arms*: 1. Donepezil 5 mg/day 2. Donepezil 10 mg/day 3. Placebo *Length of treatment*: 24 weeks active treatment followed by 6 week single-blind, placebo wash-out *Other interventions used*: none stated	*Number of patients*: Total: 818 1. Donepezil 5 mg: 271 2. Donepezil 10 mg: 273 3. Placebo: 274 *Characteristics of target population*: aged > 49 years, mild to moderately severe AD diagnosed using both DSM-III-R and NINCDS-ADRDA, MMSE scores between 10 and 26, CDR scores of 1 or 2, CT/MRI within past 6 months, females to be surgically sterilised/> 2 years post-menopausal; generally healthy with adequate vision and hearing to comply with testing *Exclusion criteria*: patients with structural lesions/significant vascular changes on scan; other psychiatric/neurological disorder; asthma; uncontrolled oncological, endocrine, gastrointestinal, renal, hepatic disorder, taking prohibited study medications *Participants*: age range 50 to 93 years; weight range 37 to 108 kg; 99% Caucasian; 42.5% male; baseline MMSE mean 20 (range 9 to 26); baseline CDR score 1.0 (84%), score 2.0 (5.6%). No significant difference between groups *Setting*: not specified	Outcomes evaluated at baseline, 6,12, 18, 24 (primary outcome) and 30 weeks *Primary outcomes*: ADAS-cog (cognition) CIBIC-plus (global function) *Secondary outcomes*: CDR-SB IDDD assessed initiation of tasks and performance using structured interview with care-giver. Self-care and complex tasks included Patient-rated QoL Adverse events including serious adverse events (patient and care-giver notified) Length of follow-up: 30 weeks

Results

ADAS-cog: statistically significant improvement in scores for both donepezil groups compared with placebo. Differences in least square means for change from baseline to 24 weeks: 5 mg vs placebo = 1.5 points ($p = 0.0021$); 10 mg vs placebo = 2.9 points ($p < 0.0001$)

CIBIC-plus: donepezil significantly increased the number of patients reported as improved at week 18 and 24 for 5 mg and 10 mg compared with placebo ($p < 0.05$). CIBIC-plus scores ≤ 3 at 24 weeks) were: placebo 14%; donepezil 5 mg 21%; donepezil 10 mg 25%

CDR-SB: statistically significant improvement in least squares mean scores for both donepezil groups compared with placebo from week 12 to end-point ($p < 0.05$). Difference in scores for: 5 mg vs placebo = 0.3 ($p = 0.0344$); 10 mg vs placebo = 0.4 ($p = 0.0033$)

IDDD: mean baseline score of 2.1 points per item (IDDD self-care score 1.5; IDDD-complex task score 2.7) indicated that patients had little/no impairment of self-care abilities and only mild impairment in execution of complex tasks. Change in total IDDD score not reported. IDDD-self-care scores: no improvement could be measured. IDDS-complex tasks: statistically significant improvement in least squares mean scores for 10 mg vs placebo at end-point ($p = 0.0072$) but not for 5 mg group vs placebo

Patient-rated QoL: high inter-patient variability. No overall treatment effects noted

Treatment wash-out: after 6 weeks wash-out period on placebo, patient scores reverted to levels similar to placebo (ADAS-cog, CIBIC-plus, CDR-SB, and IDDD)

Adverse effects:
Patients with any adverse event: placebo, 76%; 5 mg, 79%; 10 mg, 86%

Most frequently experienced adverse events were digestive system-related (nausea, diarrhoea, vomiting, anorexia) reported as: placebo, 24%; 5 mg, 26%; 10 mg, 47%. Nervous system adverse events (dizziness, confusion, insomnia) reported as: placebo, 29%; 5 mg, 36%; 10 mg, 40%

Withdrawals due to adverse events reported in: placebo, 10%; 5 mg, 9%; 10 mg, 18%. Most commonly due to nervous system-related events: placebo, 5%; 5 mg, 5%; 10 mg, 10%

continued

contd
Burns, *et al*., 1999[41]

Methodological comments
- Allocation to treatment groups: random, no details provided
- Comparability of treatment groups: groups were similar in demographic and clinical characteristics
- Blinding: double-blind, using comparable treatment regimens
- Method of data-analysis: analysis was conducted on an ITT basis (with both OC and LOCF), on fully evaluated cases and retrieved drop-out. Results were not presented consistently as point estimates of difference between active treatment and placebo with 95% CI. Assessment of efficacy contained factors for baseline score, treatment effect and centre effect. ADAS-cog, modified IDD, CDR-SB and QoL were analysed using ANCOVA with assumptions of covariance tested via Fisher's least significant difference. CIBIC-plus was analysed using Cochran–Mantel–Haenszel test
- Sample size/statistical power: sample size estimates of 250 patients per group were calculated to achieve 80% power of detecting a 0.27 point difference in mean CIBIC-plus score for each donepezil treatment group at 0.05 significance level. Sample size had to be increased to accommodate greater variance in multinational data than had been anticipated
- Attrition/drop-out: drop-outs were reported by treatment group and with reasons

General comments
- Inclusion and exclusion criteria were clearly defined though the use of strict inclusion criteria may limit the generalisibility of the results
- Outcome measures were appropriate though it was acknowledged that was the first time that the modification of the IDDD scale had been used (modified so that score < 68 represented improvement and score > 68 represented deterioration)
- There was no indication of the extent of inter-centre variability though this was reported to be greater than anticipated and no investigation of potential reasons for this variability was undertaken
- Supported by Eisai America Inc.

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 1 (comparable treatment regimens)
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 24% placebo: 20% donepezil 5 mg: 22% donepezil 10 mg: 26%

Reference and design	Intervention	Patients	Outcome measures
Greenberg, *et al.*, 2000[42] USA *Study type/design*: 2-centre, randomised placebo-controlled, double-masked, crossover *Jadad score*: 5/5	*Treatment arms*: 1. Donepezil 5 mg/day 2. Placebo *Length of active treatment*: 6 weeks *Treatment regimens*: Placebo wash-in for 6 weeks, then randomised to A or B A: Placebo treatment for 6 weeks, followed by donepezil for 6 weeks followed by placebo wash-out for 6 weeks B. Donepezil for 6 weeks, followed by placebo wash-out for 6 weeks, followed by placebo treatment for 6 weeks *Other interventions used*: none stated	*Number of patients*: Total: 60 Group A: 30 Group B: 30 *Characteristics of target population*: Men and women with probable AD (NINCDS-ADRDA Working Group), able to undergo cognitive testing defined as information-memory concentration sub-scale score of 20 or less, 6 or more years of education, fluency in English, stable doses of concomitant medication for 4 weeks before enrolment, care-giver to monitor medication use and attend all follow-up assessments *Exclusion criteria*: specific contraindications to anti-cholinesterase therapy such as history of sick sinus syndrome, other supra ventricular conduction defect, active gastrointestinal bleeding, bladder obstruction, asthma, severe obstructive pulmonary disease, hyper-sensitivity to cholinesterase inhibitor use, AChEI within previous 3 months *Participants characteristics given as mean (SD)*: age 75 years (9.5), 50% male; disease duration 3.8 (2.5) years; education 14.7 (3.5) years; MMSE score 21.8 (3.7); BDS 10.5 (4.2); ADAS-cog 18.5 (7.7). Not stated whether there was any significant difference *Setting*: memory disorder units but not specified whether inpatient/outpatient	Outcomes assessed at 6, 12, 15, 18, 21 and 24 weeks. Included start and end of donepezil and placebo treatments and after 3 weeks' wash-out *Primary outcome*: ADAS-cog scores: changes in scores categorised as improvement (negative change) vs no improvement (positive change) *Secondary outcomes*: explicit verbal recall assessed using NYU Stories Test delayed recognition sub-scale verbal fluency tested by patient generating list of words beginning with given letter care-giver rated global impression of change: categorised as mildly to markedly worsened, unchanged, or mildly to markedly improved Others: medication compliance apolipoprotein E genotype Length of follow-up: 24 weeks

Results

Not analysed ITT

Primary outcome:

ADAS-cog (based on 48/60 patients completing testing): difference between ADAS-cog scores performed using ANOVA for repeated measures. ADAS-cog score significantly improved during donepezil therapy and slightly worsened during placebo therapy. Net improvement in ADAS-cog scores (improvement indicated by lower scores) estimated by combining within-individual changes during drug and placebo = 2.17 (95% CI, 0.20 to 4.10) in response to donepezil. Number of patients in whom ADAS-cog scores improved was greater during donepezil therapy than during placebo (44% vs 19%; $p = 0.03$). Benefit of donepezil largely abated after 3 weeks wash-out. No effect on response to donepezil was associated with age, sex, level of education, disease duration, centre, and severity of dementia at baseline (BDS or MMSE)

Secondary outcomes:

Explicit verbal recall and verbal fluency: mean scores not improved with donepezil compared with placebo. Mean (SEM) verbal recall: donepezil –0.32 (0.28) vs placebo +0.23 (0.29). Mean (SEM) verbal fluency: donepezil –0.71 (0.34) vs placebo –0.27 (0.31)

Care-giver-rated global impression of change: no statistically significant difference between groups ($p = 0.34$). Improved: donepezil 24% vs placebo 23%. Worse: donepezil 27% vs placebo 36%

Adverse effects:

9 withdrew after randomisation. 2 were due to serious adverse reaction to donepezil (syncope, generalised seizure). Plus 1 patient with mild pancreatitis at end of donepezil treatment. Among study completers the most common adverse reactions to donepezil therapy were as follows: nausea (10%); diarrhoea (6%); agitation (6%). None continued after the end of donepezil treatment

continued

contd
Greenberg, *et al*., 2000[42]

Methodological comments
- Allocation to treatment groups: random, computer generated by statistician
- Comparability of treatment groups: compared but significance of difference was not assessed
- Blinding: double-blind, using comparable dummy placebo
- Method of data-analysis: results were not analysed on an ITT basis. The influence on the results of various demographic factors and the centre was assessed. Point estimates and confidence intervals were reported for the primary outcome measure
- Sample size/statistical power: sample sizes of 60 patients per group were estimated to provide 80% power of detecting a 2.5 point improvement in ADAS-cog score with donepezil compared with placebo, assuming a 10% to 20% drop-out rate
- Attrition/drop-out: 60 randomised, 51 completed treatment, data from 48 used in analysis of ADAS-cog (48 underwent ADAS cog testing after both treatments) for donepezil vs placebo. Reasons were given for 9 of the 12 who were not included in the ADAS-cog analysis

General comments
- Few exclusion criteria were applied thus making results of general applicability
- Duration of therapy was limited to 6 weeks (authors consider disease likely to be stable over this short period)
- The discussion includes consideration of the following limitations: weakness of using crossover designs in diseases with variable rates of decline; underestimation of donepezil therapy due to use of 5 mg rather than 10 mg dose; limited magnitude of donepezil effect due to the mildness of dementia in participants
- Authors also comment on the applicability of data from Phase III trials to clinical practice: research conducted in restricted populations; subjects more likely to be younger, white, male, better educated, and more affluent than those encountered in clinical practice; and improvements have been small and not present in all patients

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1 (computer generated by statistician)
Was the study described as double-blind?	1 + 1 (comparable dummy placebo)
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Reasons given for 9 who failed to complete treatment but no reasons given for lack of full ADAS-cog assessment in remaining 51 (only 48 used for ADAS-cog analysis) Taking 9 drop-outs: overall rate: 15% during placebo: 5% during donepezil: 10% group A: 16.7% group B: 13.3%

BDS, Blessed Dementia Scale

Note

Data summaries have been omitted for four unpublished studies (CIC data):

- *The Nordic Study (DON-NY-96-001)[73] (a multicentre, randomised, double-blind, placebo-controlled study carried out in Northern Europe)*
- *The Functional Survival Study (A001-312) (a randomised, double-blind, placebo-controlled study carried out in the USA)*
- *The Nursing Home Study (A001-311) (a multicentre, randomised, double-blind, placebo-controlled study carried out in the USA)*
- *The MSAD Study (DON-NY-96-324) (multicentre (32 sites), randomised, double-blind, placebo-controlled study carried out in Canada, Australia and France)*

Appendix 9

Summary of evidence of effectiveness of rivastigmine in AD

Reference and design	Research question and search strategy	Inclusion and quality criteria
Birks, *et al.*, 2000[43] *Study design*: Cochrane Systematic review (last published amendment August 2000) *NHS CRD score*: 6/6	*Aim*: to assess the clinical efficacy and safety of rivastigmine in patients with dementia of the Alzheimer's type *Search strategy*: the Cochrane Dementia Group Register of Clinical trials, CCTR (April 2000) MEDLINE (1966–May 2000), EMBASE (1980–May 2000), PsycLIT (1987–April 2000), SIGLE (1980–June 1999), ISTP (May 2000), INSIDE (June 2000), Aslib (1970–1999), US Dissertation abstracts (June 2000), ADEAR (June 2000), NRR (April 2000), Current Controlled Trials (June 2000), GlaxoWellcome Trials Database (June 2000), Centerwatch Trials Database (June 2000) were searched using the key words 'ENA 713', 'EXELON', and 'rivastigmine' in addition to the terms for controlled trials in dementia References of all identified studies were inspected Novartis was contacted for information about any published and unpublished trials	*Inclusion criteria*: Study designs: unconfounded, double-blind, placebo-controlled randomised trials. Trials with inadequate methods of randomisation were excluded Interventions: rivastigmine given at any dose administered for more than 2 weeks with parallel concomitant placebo control Population: patients diagnosed as having probable AD according to accepted criteria such as DSM-1V, NINCDS-ADRDA. Participants (from 5 of the 7 primary studies) had MMSE between 10 and 26 inclusive. Patients were excluded if they had severe and unstable illnesses (cardiovascular or pulmonary disease, unstable diabetes mellitus, peptic ulceration in past 5 years, alcohol/substance abuse) or were taking medications such as anticholinergic drugs, acetylcholine precursor health food supplements, memory enhancers, insulin and psychotropic drugs Setting: not specified Outcome measures: dependency; global impression; functional performance; cognitive function (measured by psychometric tests); behavioural disturbance; quality of life; effect on carer; death; acceptability of treatment as measured by withdrawal from trial; and safety as measured by the incidence of adverse effects (including side-effects) leading to withdrawal; institutionalisation rates Quality criteria: as per Cochrane Collaboration guidelines in which randomisation is categorised as A (adequate), B (unclear) or C (inadequate), with only those in A or B included. Details were noted of blinding, whether ITT analyses were extractable, and losses to follow-up Application of methods: inclusion criteria were applied to titles and abstracts by one reviewer. One reviewer selected trials for inclusion in the review. Quality criteria were applied by one reviewer. Data were extracted by one reviewer

continued

contd
Birks, *et al*., 2000[43]

Results
Quantity and quality of studies: 7 RCTs were identified, reports from 2 had not been published but Novartis provided data. Duration of studies was from 9 to 26 weeks. Rivastigmine doses ranged from 2 to 36 mg/day given in divided doses (bid/tid). Included fixed dose and maximum tolerated dose. There was no formal quality assessment of the included studies, although only trials that double-blind, parallel-group, placebo-controlled RCTs were included

ADAS-cog (dichotomised into people < 4 points improvement and people with ≥ 4 points improvement at 26 weeks): greater improvement was present in 6–12 mg/day group compared with placebo but not the 1–4 mg/day group. Rivastigmine (6 to 12 mg/day) vs placebo (4 RCTs, 1917 patients), OR = 0.6 (95% CI, 0.4 to 0.8), heterogeneity Z = 4.04; rivastigmine (1 to 4 mg/day) vs placebo (3 RCTs, 1293 patients) = 0.8 (95% CI, 0.6 to 1.2), heterogeneity Z = 0.98. Rivastigmine t.d.s. (2 to 12 mg/day) vs b.d. at 26 weeks (1 RCT, 455 patients) = 0.7 (95% CI, 0.4 to 1.1), heterogeneity Z = 1.53

ADAS-cog change from baseline at 26 weeks: both rivastigmine doses produced greater benefit in ADAS-cog scores compared with placebo. However, there was significant statistical heterogeneity among trials in the higher dose analysis. Rivastigmine b.d. (6 to 12 mg/day) vs placebo (4 RCTs, 1917 patients) = –2.1 (95% CI, –2.7 to –1.5), heterogeneity Z = 7.41; rivastigmine (1 to 4 mg/day) vs placebo (3 RCTs, 1293 patients) = –0.8 (95% CI, –1.5 to –0.2), heterogeneity Z = 2.54. Rivastigmine (2–12 mg/day) t.d.s. vs b.d. at 26 weeks (1 RCT, 454 patients) = –1.3 (95% CI, –2.6 to 0.0), heterogeneity Z = 1.94

MMSE: scores were improved for both rivastigmine groups compared with placebo at 26 weeks. Rivastigmine (6–12 mg/day) vs placebo (4 RCTs, 1921 patients) = –0.8 (95% CI, –1.1 to –0.5); rivastigmine (1–4 mg/day) vs placebo (3 RCTs, 1297 patients) = –0.4 (95% CI, –0.8 to –0.1). Rivastigmine (2–12 mg/day) t.d.s. vs b.d. (1 RCT, 454 patients) = –0.93 (95% CI, –1.6 to –0.3), heterogeneity Z = 2.75

CIBIC-plus (dichotomised as no change/decline vs improvement): both doses of rivastigmine showed improvement compared with placebo at 26 weeks. CIBIC-plus (no change or worse at 26 weeks): rivastigmine (6 to 12 mg/day) vs placebo (4 RCTs, 1812 patients), OR = 0.7 (95% CI, 0.6 to 0.9), heterogeneity Z = 3.39; rivastigmine (1 to 4 mg/day) vs placebo (3 RCTs, 1237 patients) = 0.7 (95% CI, 0.6 to 0.9), heterogeneity Z = 2.47. Rivastigmine (2–12 mg/day) t.d.s. vs b.d. at 26 weeks (1 RCT, 441 patients) = 0.68 (95% CI, 0.45 to 1.03), heterogeneity Z = 1.82

PDS (WMD at 26 weeks): improvement with higher dose of rivastigmine compared with placebo but not with lower dose. Rivastigmine (6 to 12 mg/day) vs placebo (4 RCTs, 1912 patients) = –2.2 (95% CI, –3.2 to –1.1), heterogeneity Z = 4.16; rivastigmine (1 to 4 mg/day) vs placebo (3 RCTs, 1288 patients) = 0.4 (95% CI, –0.9 to 1.6), heterogeneity Z = 0.60

GDS (WMS at 26 weeks): improvement for higher rivastigmine doses compared to placebo, but no the lower dose. Rivastigmine (6 to 12 mg/day) vs placebo (4 RCTs, 1923 patients) = 0.8 (95% CI, 0.6 to 0.9), heterogeneity Z = 2.57; rivastigmine (1 to 4 mg day) vs placebo (3 RCTs, 1296 patients) = 0.9 (95% CI, 0.7 to 1.1), heterogeneity Z = 0.87

Withdrawals: no significant difference between the lower rivastigmine groups and placebo but increased withdrawals in the high dose rivastigmine group compared with placebo

Withdrawals before end of treatment at 12 weeks: rivastigmine (6 to 12 mg/day) vs placebo (1 RCT, 266 patients) = 2.6 (95% CI, 1.2 to 5.7) heterogeneity Z = 2.39; rivastigmine (1 to 4 mg/day) vs placebo (1 RCT, 269 patients) = 2.15 (95% CI, 0.95 to 4.89) heterogeneity Z = 1.83

Withdrawals before end of treatment at 18 weeks: rivastigmine (6 to 12 mg/d b.d.) vs placebo (1 RCT, 69 patients) = 4.0 (95% CI, 1.3 to 12.3), heterogeneity Z = 2.43

Withdrawals before end of treatment at 26 weeks: rivastigmine (6 to 12 mg/day) vs placebo (4 RCTs, 1920 patients) = 2.4 (95% CI, 2.0 to 3.0), heterogeneity Z = 8.22; rivastigmine (1 to 4 mg/day) vs placebo (3 RCTs, 1290 patients) = 1.01 (95% CI, 0.75 to 1.34), heterogeneity Z = 0.04. Rivastigmine (2 to12 mg/day) t.d.s. vs b.d. (1 RCT, 456 patients) = 0.6 (95% CI, 0.4 to 1.0), heterogeneity Z = 1.82

Withdrawals due to adverse events: increased withdrawals due to adverse events in the higher dose rivastigmine groups compared with placebo but not in lower dose groups compared with placebo. Withdrawals due to adverse events at 26 weeks: rivastigmine (6–12 mg/day) vs placebo (4 RCTs, 1920 patients) = 3.0 (95% CI, 2.3 to 3.8) heterogeneity Z = 8.80; rivastigmine (1–4 mg/day) vs placebo (3 RCTs, 1290 patients) = 1.0 (95% CI, 0.7 to 1.5), heterogeneity Z = 0.12

Withdrawals due to serious adverse effects before end of treatment at 26 weeks: rivastigmine (6 to 12 mg /day) vs placebo (4 RCTs, 1920 patients) = 2.4 (95% CI, 2.0 to 3.0), heterogeneity Z = 8.22; rivastigmine (1 to 4 mg/day) vs placebo (3 RCTs, 1290 patients) = 1.01 (95% CI, 0.75 to 1.34), heterogeneity Z = 0.04

continued

contd
Birks, *et al.*, 2000[43]

Methodological comments

- Search strategy: electronic databases, references, experts and industry were consulted for published and unpublished studies
- Participants: only participants with serious illness or particular medications were excluded, thus subjects are likely to be representative of the general population
- Inclusion/exclusion criteria: appropriately defined in terms of intervention, participants and outcomes assessed. Only applied by one reviewer in the updated version, with no checking
- Quality assessment: although only double-blind, parallel-group, placebo-controlled RCTs were included, no assessment was made of their adequacy. Assessment by one authors, with no checking
- Method of synthesis: meta-analysis was performed using ITT results (although OC and OC + RDO were also calculated) but the authors point out that methods used to handle missing data were not reported. Differences in drop-out rates between treatment groups were included in the analysis. Results were reported as point estimates with 95% CI. Heterogeneity was assessed statistically. The authors justified the use of fixed models to analyse ADAS-cog scores despite heterogeneity on the grounds that only 4 trials were included. The authors correctly advised caution in interpreting these results. Potential causes of heterogeneity among the trials reporting ADAS-cog scores were briefly discussed

General comments

- The available evidence shows a small but statistically significant benefit for high dose rivastigmine on cognitive function, behaviour and rated severity of dementia. There appear to be clinically and statistically significant improvements in CIBIC-plus. At lower doses there were significant differences in CIBIC-plus at 26 weeks. Withdrawal rates due to adverse events were predictable
- The systematic review warns of the problems associated with the use of incomplete data sets with the different methods of analysis (ITT, LOCF, OC and OC + RDO) including no details of methods used to handle missing data in reported ITT analysis, misleading results from LOCF analysis resulting from higher withdrawals in higher dose groups and omission of OC analysis from some reports
- Open-label phase extensions of these trials require caution in interpretation due to randomised double-blind conditions no longer applying, lack of control group, rate of decline in placebo patients from extrapolation from the randomised phase and may be misleading
- All 7 trials were supported by Novartis and had similar inclusion criteria

Quality assessment for systematic reviews (NHS CRD criteria)

Question	**Score**
1. Does the review answer a well-defined question?	1
2. Was a substantial effort made to search for all the relevant literature?	1
3. Are the inclusion/exclusion criteria reported and are they appropriate?	1
4. Is the validity of included studies adequately assessed?	1
5. Is sufficient detail of the individual studies presented?	1
6. Have the primary studies been combined or summarised appropriately?	1

RDO, retrieved drop-out

Reference and design	Research question and search strategy	Inclusion and quality criteria
Wolfson, *et al*., 2000[36] Canada *Study design*: systematic review *NHS CRD score*: 5/6	*Aim*: to assess and compare the evidence for the clinical efficacy of individual therapies for AD *Search strategy*: electronic databases included Applied Science and Technology, CINAHL, Core Biomedical Collection, Core Biomedical Collection III, HealthSTAR, MEDLINE, PsycINFO, Cochrane Library and multi-media. Review articles were handsearched for references *Search terms*: 'Rivastigmine', 'Donepezil', 'Alzheimer's Disease', 'Drug Therapy'	*Inclusion criteria* Study design: published trials that have the methodological integrity to provide the best evidence on donepezil, galantamine and rivastigmine Intervention: donepezil, galantamine or rivastigmine versus placebo Population: patients with a diagnosis of probable AD using NINCDS/ADRDA diagnostic criteria Setting: not specified Outcome measures: not specified *a priori* but included ADAS-cog, CGIC, CIBIC-plus (including care-giver-supplied info) CDR-SB and QoL as secondary outcome measures, MMSE as secondary cognitive performance outcome, the IDDD, PDS Quality criteria: methodological quality of the trials was assessed using the Jadad 6-item scale, with those ≥ 5 on Jadad scale being included Application of methods: it is unclear how inclusion criteria were applied. Three reviewers independently assessed the trials for quality, with a consensus meeting to resolve any differences. It is unclear how the data were extracted

Results

Rivastigmine studies: 2 placebo-controlled, double-blind parallel multicentre trials of 26 weeks. Assessment was carried out at baseline, 12 weeks, 18 weeks, 26 weeks or early termination. 699 patients in the US trial (22 sites) and 725 patients in the European/North American trial (45 sites). Patient characteristics could not be adequately compared. Dose titration phase achieved maximum tolerated doses of 3.5 to 4 mg/day for low-dose group and 9.7 to 10.4 mg/day high-dose group. Analysis on ITT basis using the LOCF approach and an observed case analysis (OC) that included all patients. Both trials used a dosing approach aimed at determining the maximum tolerated dose for each patient

Quality assessment: the Jadad scores for the 4 trials on donepezil were all scored between 6 and 7. The Jadad scores for the 2 rivastigmine trials were 5–6 and 8

ADAS-cog: in the US rivastigmine trial the placebo group (ITT analysis) was seen to decline significantly with an average increase in score of 4.09 points (95% CI, 3.32 to 4.86). The 2 treatment groups showed a significantly smaller decline of 2.36 (95% CI, 1.59 to 3.13) points on average in the low-dose group and 0.31 (95% CI, –0.46 to 1.08) points on average in the high-dose group. In the European/North American trial the placebo participants deteriorated only 1.34 points on average (95% CI, 0.41 to 2.19) in the ITT analysis. Participants in the high-dose group improved an average of 0.26 points (95% CI, –1.06 to 0.66) according to ITT analysis. Comparing the change in the placebo group with that in the high-dose group yielded a statistically significant 1.6 point difference in favour of the high-dose group ($p < 0.1$, ITT) or 2.58 points ($p < 0.001$, OC). For the low-dose group, there is evidence of decline (mean decline of 1.37 points ITT, 95% CI, 0.53 to 2.27, mean decline of 1.24 points OC, 95% CI, 0.29 to 2.31)

CIBIC-plus scale: for the US rivastigmine trial at 26 weeks, the average change from baseline in the high-dose group was 0.2 (95% CI, 0.04 to 0.36) indicating an overall worsening in global function. The change from baseline in the low-dose group was 0.23 (95% CI, 0.07 to 0.39). The decline in the placebo group is reflected in an average change of 0.49 (95% CI, 0.33 to 0.65) points. Overall, the high-dose group was found to have statistically significant less deterioration in global function than the placebo group (average difference of –0.29 points with a 95% CI from –0.51 to –0.07). From the ITT analyses of the European study the high-dose group improved on average with score of 3.91 (95% CI, 3.71 to 4.09) whereas both the low-dose group and the placebo group deteriorated on average with CIBIC plus scores of 4.24 (95% CI, 4.02 to 4.38) and 4.38 (95% CI, 4.22 to 4.58) respectively

PDS: in the US study (ITT analysis) the high-dose group declined an average of 1.52 points, the low-dose group declined an average of 5.19 points which was similar to the placebo group which declined an average of 4.9 points. In the European study (ITT analysis) the high-dose group improved on average, the low-dose group declined an average of 3.37 points and the placebo group declined an average of 2.18 points. 29% of the high-dose group was found to have improved 10% or more on the PDS, as compared to 20% of the low-dose group and 19% of the placebo group. In the LOCF analysis, the difference in the proportion of high dose patients and placebo patients who improved 10% or more on the PDS was 13%. The use of the LOCF analysis may have resulted in an overestimation of the improvement in the high-dose group

Adverse effects and drop outs:

Frequently reported (≥ 5%) adverse effects for rivastigmine are: fatigue, dizziness, somnolence, nausea, vomiting, anorexia, sweating, asthenia, dyspepsia, diarrhoea, abdominal pain, malaise

continued

contd
Wolfson, *et al.*, 2000[36]

Methodological comments
- Search strategy: sources and limitations were adequately discussed
- Participants: characteristics of participants are discussed and effects on outcomes noted
- Inclusion/exclusion criteria: Not explicitly stated *a priori* and method of application not discussed
- Quality assessment: Jadad 6-item score used, but limited discussion of scores for specific studies
- Method of synthesis: narrative synthesis, due to differences between the studies

General comments
- Trials on rivastigmine were supported by Novartis
- Limited reporting on limitations and clinical relevance of the evidence
- All of the trials used the LOCF approach for drop-outs and this may have resulted in an overestimation of a treatment effect
- Reporting differences in the rivastigmine trials hindered direct comparison of patients characteristics across treatment groups. In the rivastigmine trials the instruments (ADAS-cog, CIBIC-plus and the PDS) appear to have been used appropriately
- For the rivastigmine trials, in the placebo and low-dose group between 13% and 16% of the patients did not complete the trial, in the high-dose group between 43% and 52% of the patients did not complete the trial. In the high-dose group this was mostly attributed to adverse effects. The heavy losses in both rivastigmine trials is troubling and hinders conclusion regarding the efficacy of this medication in relation to cognitive stability or improvement

Quality assessment for systematic reviews (NHS CRD criteria)

Question	**Score**
1. Does the review answer a well-defined question?	1
2. Was a substantial effort made to search for all the relevant literature?	1
3. Are the inclusion/exclusion criteria reported and are they appropriate?	0
4. Is the validity of included studies adequately assessed?	1
5. Is sufficient detail of the individual studies presented?	1 (drop-outs reported)
6. Have the primary studies been combined or summarised appropriately?	1

Reference and design	Research question and search strategy	Inclusion and quality criteria
Livingston, *et al.*, 2000[37] UK *Study design*: systematic review *NHS CRD score*: 4/6	*Aim*: to assess the clinical efficacy of cholinesterase inhibitors (donepezil, rivastigmine and tacrine) for people with AD *Search strategy*: electronic databases searched included MEDLINE (1966–1998), EMBASE (1994–1999) and PsycLIT (1974–1998) using keywords cholinesterase and placebo and dementia. No language restrictions	*Inclusion criteria* Study design: double-blind, randomised and placebo-controlled including > 10 patients and lasting > 1 day. Crossover and open label extension studies were excluded Intervention: cholinesterase inhibitors Population: patients with a diagnosis of probable AD. Studies including other dementia were excluded Setting: not specified Outcome measures: Not specified *a priori* but included ADAS-cog, CIBIC-plus, CIBI, MMSE, IDDD, and PDS Quality criteria: not stated Application of methods: not stated

Results

- ADAS-cog improvement ≥ 4 (1–4 mg), NNT –10 (95% CI, –13 to 19)
- CIBIC-plus improvement (1–4 mg), NNT 10 (95% CI, 6,44)
- PDS (ADL) improvement > 10% (1–4 mg), NNT ∞ (95% CI, –14 to 15)
- ADAS-cog improvement ≥ 4 (6–12 mg), NNT 13 (95% CI, 7 to 111)
- CIBIC-plus improvement (6–12 mg), NNT 6 (95% CI, 4 to 11)
- PDS (ADL) improvement > 10% (6–12 mg), NNT 10 (95% CI, 6 to 42)
- ADAS-cog no deterioration (6–12 mg), NNT 4 (95% CI, 3 to 6)
- ADAS-cog decline ≥ 4 (6–12 mg), NNT 5 (95% CI, 3 to 8)
- ADAS-cog decline ≥ 7 (6–12 mg), NNT 5 (95% CI, 4 to 7)
- CIBIC-plus improvement (6–12 mg), NNT 12.5 (95% CI, –179 to 6) (Note: figures checked and re-calculated to –12 (95% CI, ∞ to –5) suggesting NNT should read –12.5)
- CIBIC-plus improvement (1–4 mg), NNT 12 (95% CI, 6 to 273)
- PDS (ADL) improvement > 10% (6–12 mg), NNT 10 (95% CI, 6 to 70)

Methodological comments

- Search strategy: sources and limitations were adequately discussed
- Participants: limited discussion of characteristics of participants or effects on outcomes noted
- Inclusion/exclusion criteria: adequately stated although method of application not discussed
- Quality assessment: not stated
- Method of synthesis: narrative synthesis based on the calculation of NNTs

General comments

- Studies show small numbers of patients need to be treated to ameliorate cognitive and non-cognitive symptoms or postpone deterioration
- Low doses produce no improvement in some cognitive outcomes

Quality assessment for systematic reviews (NHS CRD criteria)

Question	Score
1. Does the review answer a well-defined question?	1
2. Was a substantial effort made to search for all the relevant literature?	1
3. Are the inclusion/exclusion criteria reported and are they appropriate?	1
4. Is the validity of included studies adequately assessed?	0
5. Is sufficient detail of the individual studies presented?	0
6. Have the primary studies been combined or summarised appropriately?	1

Reference and design	Intervention	Patients	Outcome measures
Sramek, *et al*., (1996)[44] USA *Study type/design*: double-blind, randomised, parallel-group, safety/tolerability study (Phase I) *Jadad score*: 4/5	*Treatment arms*: 1. ENA713* b.d. 2. ENA713 t.d.s. 3. Placebo *Length of treatment*: 10 weeks (composed of 9 weeks fixed dose escalation as follows: days 1–3, 2 mg/day; days 4–7, 3 mg/day; week 2, 4 mg/day; week 3, 5 mg/day; week 4, 6 mg/day; week 5, 7.25 mg/day; week 6, 8.5 mg/day; week 7, 10 mg/day; week 8–9, 12 mg/day, week 10, treatment-free wash-out) *Other interventions used*: not stated	*Number of patients*: Total = 50 1. ENA713 b.d.: 20 2. ENA713 t.d.s.: 20 3. Placebo: 10 *Characteristics of target population*: outpatients diagnosed with probable AD on NINCDS-ADRDA; MMSE score 10 to 26 who have not had medical, neurological or psychiatric disorders (other than AD) that may affect assessment of dementia *Exclusion*: patients with severe cardiovascular or pulmonary disease, unstable diabetes, peptic ulceration within 5 years, evidence of alcohol or substance abuse, or disease of a organ system affect results or place patients at risk, or had taken investigational drugs in last 4 weeks, any drugs with toxicity for major organs in last 3 months, tranquillisers within 2 weeks, antidepressants in past month, neuroleptics in past 2 months or any concomitant drug interacting with ENA713 were excluded *Participants' characteristics*: men n = 22, women n = 28; mean age 68 years (range 45–90 years) *Setting*: outpatient and inpatient	Outcomes assessed at screening, baseline, weekly through 4 weeks as outpatients, weeks 5–8 as inpatients for administration evaluated on discharge, weeks 9–10 as outpatients *Primary outcomes*: physical examinations, electrocardiography, vital signs, clinical laboratory tests and volunteered and observed adverse events, as well as a diary of adverse events by patients or care-giver *Secondary outcomes*: medical and treatment histories, modified Hachinski ischemic score, drug and hepatitis screens, a chest X-ray, CT or MRI and an electroencephalogram Length of follow-up: 10 weeks

Results

- Withdrawals due to adverse events: overall 5/50 patients (10%); ENA713 3/40 patients (7.5%); placebo: 0/10 patients (0%)
- Adverse events in at least 15% of patients on either ENA713 regimen: headache (placebo 70%, b.d. 65% (p = ns), t.d.s. 65% (p = ns)); nausea (placebo 10%, b.d. 40% (p = ns), t.d.s. 55% (p < 0.05)); dizziness (placebo 30%, b.d. 40% (p = ns), t.d.s. 40% (p = ns)); diarrhoea (placebo 30%, b.d. 40% (p = ns), t.d.s. 35% (p = ns)); vomiting (placebo 20%, b.d. 30% (p = ns), t.d.s. 25% (p = ns)); flatulence (placebo 10%, b.d. 30% (p = ns), t.d.s. 15% (p = ns)); agitation (placebo 0%, b.d. 30% (p < 0.10), t.d.s. 0% (p = ns)); fatigue (placebo 0%, b.d. 25% (p = ns), t.d.s. 30% (p < 0.10)); abdominal pain (placebo 40%, b.d. 25% (p = ns), t.d.s. 25% (p = ns)); rhinitis (placebo 40%, b.d. 20% (p = ns), t.d.s. 25% (p = ns)); coughing (placebo 30%, b.d. 20% (p = ns), t.d.s. 15% (p = ns)); myalgia (placebo 0%, b.d. 20% (p = ns), t.d.s. 5% (p = ns)); urinary incontinence (placebo 0%, b.d. 20% (p = ns), t.d.s. 0% (p = ns)); dyspepsia (placebo 30%, b.d. 15% (p = ns), t.d.s. 25% (p = ns)); sweating (placebo 0%, b.d. 10% (p = ns), t.d.s. 25% (p = ns)); asthenia (placebo 0%, b.d. 10% (p = ns), t.d.s. 25% (p = ns)); hot flushes (placebo 0%, b.d. 0% (p = ns), t.d.s. 20% (p = ns))
- Safety monitoring: laboratory values, ECGs or vital signs showed no clinically significant differences between groups

Methodological comments

- Allocation to treatment groups: random, method not stated
- Blinding: double-blind, using identical dosing, all patients received 3 doses daily
- Comparability of treatment groups: limited information provided
- Method of data analysis: chi-squared and Fisher's Exact tests for homogeneity of treatment groups, treatment differences by Fisher's Exact tests, one-way ANOVA and pair-wise tests for between treatment differences
- Sample size/statistical power: not stated
- Attrition/drop-out: appropriately stated with reasons

continued

contd
Sramek, *et al.*, (1996)[44]

General comments
- Supported by Sandoz Pharmaceuticals

Quality assessment for systematic reviews (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 5/50 patients (10%) 1. ENA713 3/40 patients (7.5%) 2. Placebo: 2/10 patients (20%)

* *ENA713 = rivastigmine*

Reference and design	Intervention	Patients	Outcome measures
Agid, *et al.*, 1998[45] Multinational (Austria, Belgium, Czechoslovakia, Denmark, Finland, France, Germany, Ireland, Norway, Sweden, Switzerland, UK) *Study type/design*: multicentre (54 centres), placebo-controlled, double-blind RCT *Jadad score*: 4/5	*Treatment arms*: 1. Rivastigmine 4 mg/day 2. Rivastigmine 6 mg/day (2 divided doses) 3. Placebo *Length of treatment*: 13 weeks Titration to target dose over 3 weeks, maintenance for 10 weeks followed by 2 week placebo wash-out *Other interventions used*: none	*Number of patients*: Total: 402 enrolled Rivastigmine 4 mg/day: 136 Rivastigmine 6 mg/day: 133 Placebo: 133 *Characteristics of target population*: mild to moderate dementia using criteria for AD defined in DSM III and probable AD according to NINCD-ADRDA; all medication of cognitive enhancing potential withdrawn for at least 3 weeks Medications for non-cognitive aspects of AD (hypnotics) allowed provided were short acting. Concomitant drugs continued *Participants' characteristics*: mean age (SD) 4 mg/day 68.62 (8.64), 6 mg/day 68.68 (7.85), placebo 70.80 (8.58); age range 50 to 90 years; 42% male. Normal signs, living with reliable care-giver and capable of ingesting oral medication *Setting*: not specified	Outcomes assessed at baseline and 13 weeks CGIC responders (defined as patient with scores of 1 or 2; failure defined as scores of 3 to 7) Fuld Object–memory Evaluation Digit Symbol Substitution Test Benton retention Test Trail Making test MMSE Nurse Observation Scale for Geriatric Patients Assessment of individual daily activities by patients and care-givers Safety monitoring: diverse reactions; physical examination, vital signs, blood chemistry, haematology, urinalysis, and ECG Length of follow-up: 15 weeks; reports that at end of trial patients could enrol in an extended phase trial

Results

CGIC: statistically significant higher proportion of 6 mg patients than placebo patients had successful outcome (42.7% vs 29.91%; $p = 0.05$). No statistically significant difference between 4 mg vs placebo (31.53 % vs 29.91%; p = ns)

Digit Symbol Substitution Test, mean (± SD):
4 mg vs placebo: 7 weeks, 2.1 (± 5.8) vs 0.1 (± 7.4), p = ns; 13 weeks, 1.7 (± 5.1) vs 0.5 (± 6.9), p = ns
6 mg vs placebo: 7 weeks, 2.0 (± 5.4) vs 0.1 (± 7.4), $p \leq 0.05$; 13 weeks, 2.8 (± 8.1) vs 0.5 (± 6.9), $p \leq 0.05$

Fuld Object–memory Evaluation:
Storage test
4 mg/day vs placebo: 7 weeks, 2.2 (± 7.3) vs 0.0 (± 6.2), $p \leq 0.01$; 13 weeks, 0.4 (± 6.2) vs –0.9 (± 5.5), $p \leq 0.05$
6 mg/day vs placebo: 7 weeks, 2.0 (± 6.6) vs 0.0 (± 6.2), $p \leq 0.05$; 13 weeks, 0.7 (± 6.2) vs –0.9 (± 5.5), $p \leq 0.05$
Total retrieval
4 mg/day vs placebo: 7 weeks, 1.7 (± 5.3) vs 0.5 (± 4.6), $p \leq 0.05$
6 mg/day vs placebo: 7 weeks, 2.4 (± 4.8) vs 0.5 (± 4.6), $p \leq 0.005$; 13 weeks, 1.1 (± 4.2) vs 0.1 (± 4.3), $p \leq 0.05$

NOSGER, MMSE, Benton Visual Retention and Trail Making test: show no significant statistical difference between interventions

Adverse effects:
9% withdrew due to adverse events (placebo 4%; rivastigmine low dose 10%; rivastigmine high dose 12%). Incidence of most common side-effects as follows: nausea (placebo 6%; rivastigmine low dose 17%; rivastigmine high dose 31%); vomiting (placebo 3%; rivastigmine low dose 10%; rivastigmine high dose 18%); diarrhoea (placebo 2%; rivastigmine low dose 7%; rivastigmine high dose 12%); abdominal pain (placebo 5%; rivastigmine low dose 6%; rivastigmine high dose 7%); dizziness (placebo 7%; rivastigmine low dose 6%; rivastigmine high dose 20%); headache (placebo 6%; rivastigmine low dose 4%; rivastigmine high dose 13%)

continued

contd
Agid, *et al*., 1998[45]

Methodological comments
- Allocation to treatment groups: random, method not adequately described
- Comparability of treatment groups: only age compared, no other data
- Blinding: double-blind, using comparable dummy placebo
- Method of data-analysis: not ITT; observed cases were included 331 patients (82%); 4 mg 119 (87.5%); 6 mg 113 (85%); placebo 125 (94%). Point estimates and CIs were not presented
- Sample size/statistical power: not stated
- Attrition/drop-out: withdrawals were described by treatment group with reasons

General comments
- Inclusion and exclusion criteria were stated. Exclusion criteria were few, hence increasing generalisability
- No mention was made of assessment of centre effect and any evaluation of centre/treatment interaction
- Supported by Novartis Pharma AG

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 0 (patients assigned randomisation number by the investigator in numerical order according to a list generated by Novartis)
Was the study described as double-blind?	1 + 1 (comparable dummy placebo)
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 11% Rivastigmine low dose: 13% Rivastigmine high dose: 15% Placebo: 6%

Reference and design	Intervention	Patients	Outcome measures
Corey-Bloom, *et al.*, 1998[46] USA *Study type/design:* multicentre (22 centres), double-blind, placebo-controlled RCT *Jadad score*: 5/5	*Treatment arms*: 1. Rivastigmine 1 to 4 mg/day (low dose). Mean 3.5 mg/day 2. Rivastigmine 6 to 12 mg/day (high dose). Mean 9.7 mg/day 3. Placebo *Length of treatment*: 26 weeks (composed of 7 weeks fixed dose titration phase followed by flexible dose maintenance phase from weeks 8 to 12; dose increased to maximum tolerated dose) *Other interventions used*: none	*Number of patients*: Total: 699 Rivastigmine (low dose): 233 Rivastigmine (high dose): 231 Placebo: 235 *Characteristics of target population*: aged 45 to 89 years of non-childbearing potential, criteria for dementia according to DSM-IV, probable AD according to NINCDS-ADRDA; mild to moderate impairment judged by MMSE score 10 to 26; head CT/MRI scan within 12 months of entry; responsible care-giver *Exclusion criteria*: insulin-dependent diabetes; severe and unstable medical illness (those with other concomitant diseases were included); anticholinergic drugs, memory enhancers, psychotropic drugs (other than occasional use of chloral hydrate for agitation/insomnia) *Participants' characteristics*: mean age 74.5 years; 39% men; 96% Caucasian; 42% mild dementia; 94% had concomitant illness; 93% taking a variety of other medications; disease duration ranged from 3 to 180 months (mean approx. 39 months) *Setting*: not specified	Outcomes assessed at baseline, weeks 12, 18 and 26/at termination ADAS-cog CIBIC-plus PDS MMSE Global Deterioration Scale Safety monitoring: physical examination, ECG, vital signs, laboratory tests Adverse events Length of follow-up: 26 weeks

Results

Only ITT analysis given below

ADAS-cog: statistically significant improvement in ADAS-cog scores for rivastigmine (high dose) compared to placebo: 3.78 (95% CI, 2.69, 4.87; $p < 0.001$)

CIBIC-plus: statistically significant improvement in CIBIC-plus scores for rivastigmine (high dose) compared with placebo: –0.29 (95% CI, –0.51 to –0.07; $p < 0.010$)

PDS: statistically significant improvement in PDS scores for rivastigmine (high dose) compared with placebo: 3.38 (95% CI, 1.51 to 5.25; $p < 0.001$)

MMSE: ITT analysis not reported. For OC analysis: patients receiving placebo deteriorated by 0.79 on MMSE, while high dose improved by 0.30 over baseline

Global Deterioration Scale: ITT analysis – statistically significant improvement in GDS scores for rivastigmine (high dose) compared with placebo: 0.19 (95% CI, 0.06 to 0.32: $p < 0.030$)

Adverse effects:
Withdrawal due to adverse event: placebo, 7%; rivastigmine (low dose), 8%; rivastigmine (high dose), 29%

The following adverse reactions (reported as placebo vs rivastigmine (low dose) vs rivastigmine (high dose) were significantly more common in the higher dose rivastigmine groups than in placebo during the maintenance phase: dizziness (4% vs 8% vs 14%); nausea (3% vs 8% vs 20%); vomiting (2% vs 5% vs 16%); dyspepsia (1% vs 6% vs 5%) and sinusitis (1% vs 1% vs 4%). Nausea, vomiting and dyspepsia were significantly more common in the lower rivastigmine group compared with placebo. The majority of nausea and vomiting was mild in intensity, occurred during the dose titration phase (when dose reduction was not allowed) and resolved without treatment

Weight decreases (of ≥ 7%) were significantly more common in rivastigmine groups compared with placebo: rivastigmine (low dose) vs placebo: 6% vs 2% ($p < 0.05$) ; rivastigmine (high dose) vs placebo: 21% vs 2% ($p < 0.001$)

No consistent or clinically significant drug related laboratory abnormalities, ECG, vital signs, or laboratory tests were noted

continued

contd
Corey-Bloom, *et al*., 1998[46]

Methodological comments

- Allocation to treatment groups: random, independent of study group
- Comparability of treatment groups: baseline comparability was assessed and results presented
- Blinding: double-blind, comparable dummy placebo
- Method of data-analysis: analysis performed on 3 data sets: ITT (all randomised patients); traditional LOCF including randomised patient with at least one evaluation while on study medication; and OC including randomised patient with at least one evaluation while on study medication at designated assessment times. Results were presented for ITT and OC analysis. Authors report that results from all 3 types of analysis were similar. No mention was made of inter-centre variability
- Sample size/statistical power: sample size estimated at 200 per group to achieve power of 90% in detecting at least a 3-point improvement on ADAS-cog and an increase in the responder rate from 15% to 30% on CIBIC-plus
- Attrition/drop-out: reasons for withdrawal were presented by treatment group. Reports that out of 925 patients, 226 (24%) were not eligible. Reasons for non-eligibility were not reported

General comments

- The inclusion and exclusion criteria were clearly defined and participants included those with co-existing disease and on concomitant drug therapy thus increasing the general applicability of results
- Supported by Novartis Pharmaceuticals

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1 (randomisation adequate)
Was the study described as double-blind?	1 + 1 (comparable dummy placebo)
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 22% Rivastigmine (low dose): 15% Rivastigmine (high dose): 35% Placebo: 16%

Reference and design	Intervention	Patients	Outcome measures
Forette, *et al*., 1999[47] Multinational (Belgium, Canada, France, Norway, UK) *Study type/design*: multicentre (11 centres), double-blind, placebo-controlled RCT *Jadad score*: 2/5	*Treatment arms*: 1. Rivastigmine b.d. mean 9.6 mg/day 2. Rivastigmine t.d.s. mean 10.1 mg/day 3. Placebo Rivastigmine increased from 2 to 12 mg/day to reach maximal tolerated dose *Length of treatment*: 18 weeks (composed of 10 weeks dose titration phase followed by 8 weeks maintenance phase) *Other interventions used*: patients developing nausea and/or vomiting given domperidone 10 to 20 mg t.d.s./if ineffective metoclopramide 10 mg t.d.s. 35% of those on rivastigmine appear to have had anti-emetics	*Number of patients*: Total: 114 Rivastigmine (b.d.): 45 Rivastigmine (t.d.s.): 45 Placebo: 24 *Characteristics of target population*: mild to moderate dementia defined by DSM-III criteria plus diagnosis of probable AD according to NINCDS-ADRDA; MMSE score 10 to 26 *Exclusion criteria*: significant medical, neurological or psychiatric disorder *'Valid' participants characteristics given as mean (SD)*: age 71.2 (7.5) years; ADAS-cog 23.1 (9.6); duration of dementia 3.6 (2.4) units not stated; MMSE score 19.5 (3.7). Not stated whether these were significant differences Patients unable to tolerate doses of 6 mg/day were withdrawn from the study *Setting*: not specified	Outcomes assessed at 4, 10 and 18 weeks Primary and secondary outcomes not specified ADAS-cog Wechsler logical memory test (immediate and delayed recall) Digit span test Word fluency CIBIC-plus Nurses Observation Scale for Geriatric Patients completed by next of kin/carer Safety monitoring: physical examination, ECG, vital signs, laboratory tests Adverse events Length of follow-up: 18 weeks

Results

Results are based on those completing the study as per protocol

ADAS-cog: non significant improvement in ADAS scores on rivastigmine b.d. compared with placebo ($p = 0.054$, Wilcoxon test)

CIBIC plus: significantly more patients were improved (scores of 1,2 or 3) in rivastigmine b.d. group compared with placebo (57% vs 16%; $p = 0.027$). Patients on t.d.s. were not significantly different (36%)

Nurses Observation Scale for Geriatric patients: out of 6 domains tested statistically significant improvement was only seen in rivastigime vs placebo for memory: rivastigmine b.d. vs placebo (–0.7 vs 1.3; $p = 0.037$); rivastigmine t.d.s. vs placebo (–1.0 vs 1.3; $p = 0.014$)

Other measures: no significant differences were reported for rivastigmine vs placebo

Adverse effects (analysis on ITT basis):
Rates of withdrawal due to adverse reactions: rivastigmine b.d. 20%; rivastigmine t.d.s. 11%; placebo 4%

Most frequent adverse reactions were as follows (reported as rivastigmine b.d. vs rivastigmine t.d.s. vs placebo): nausea (58% vs 58% vs 8%); vomiting (38% vs 31% vs 4%); dizziness (27% vs 9% vs 0%); anorexia (18% vs 16% vs 0%); headache (16% vs 20% vs 4%)

13 serious adverse reactions occurred. 4 considered as possibly due to study medication (weight loss and hyper salivation, nausea and vomiting, bradycardia, and abdominal pain)

No statistically significant or clinically relevant drug-related laboratory abnormalities, ECG, vital signs or laboratory tests were noted

continued

contd
Forette, *et al.*, 1999[47]

Methodological comments

- Allocation to treatment groups: random, method not stated
- Comparability of treatment groups: no comment was made on the statistical significant/otherwise of difference in baseline characteristics between treatment groups though details of some characteristics were presented
- Blinding: double-blind, but no detail of methods
- Method of data-analysis: efficacy analysis based on 'valid' patient population defined as those who completed study in accordance with the protocol, that is not ITT. Thus analysis based on 23/45 (51%) randomised to rivastigmine b.d.; 28/45 (62%) randomised to rivastigmine t.d.s.; and 19/ 24 (79%) randomised to placebo. Pair-wise comparisons using Wilcoxon and Kruskall–Wallis test. Results were not reported as point estimate of difference between treatment groups with 95%CI. Safety analysis conducted on ITT basis
- Sample size/statistical power: not stated, but appeared to be small sample
- Attrition/drop-out: drop-out rates were high. Reasons for all drop-outs were not reported (reasons were given for 29 out of the 44 who did not complete the protocol). There was no discussion of the difference in significance levels of the two rivastigmine regimes

General comments

- The inclusion criteria were clearly defined. Excluded were patients with 'significant medical, neurological or psychiatric disorder.' but these patients were not defined further. Characteristics of patients did not include number with co-existing medical conditions or number of concurrent drug therapy
- Supported by Novartis Pharma

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 0
Was there a description of withdrawals and dropouts?	0 (reasons not reported for all)
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 39% Rivastigmine b.d.: 49% Rivastigmine t.d.s.: 38% Placebo: 21%

Reference and design	Intervention	Patients	Outcome measures
Rosler, *et al*., (1999)[48] Europe and North America *Study type/design*: multicentre (45 centres), double-blind, placebo-controlled, RCT *Jadad score*: 5/5	*Treatment arms*: 1. Rivastigmine 1 to 4 mg/day. Mean 3.7 mg/day (lower dose) 2. Rivastigime 6 to 12 mg/day. Mean 10.4 mg/day (higher dose) 3. Placebo *Length of treatment*: 26 weeks *Other interventions used*: none stated	*Number of patients*: Total: 725 1. Rivastigmine (lower dose): 243 2. Rivastigmine (higher dose): 243 3. Placebo: 239 *Characteristics of target population*: aged 50 to 85 and unable to bear children, met criteria for AD defined in DSM-IV and NINCD-ADRDA; MMSE score from 10 to 26; responsible care-giver *Excluded*: severe/unstable cardiac disease, severe obstructive pulmonary disease or other life threatening conditions; those taking anticholinergic drugs, insulin, memory enhancers, psychotropic drugs (small doses of short acting benzodiazepines, chloral hydrate, or haloperidol allowed) *Participants' characteristics*: 41% men; mean age 72 years (range 45 to 95); 97% white; mean disease duration 39 months; 41% had mild AD; 80% reported other prior/current medical conditions; 81% taking other concomitant drug at baseline; ADAS-cog scores ranged from 3.3 to 60.7; PDS scores ranged from 7.1 to 94.6. Demographic and disease characteristics were comparable across groups *Setting*: recruited from community	Outcomes assessed at baseline, 12, 18 and 26 weeks or at early withdrawal from trial ADAS-cog CIBIC-plus PDS MMSE GDS Safety evaluations: physical examinations, ECG, vital signs, laboratory testing, adverse events Length of follow-up: 26 weeks

Results

Results were presented as changes from baseline with 95% CI and *p* values of comparison between active treatment and placebo

ADAS-cog: statistically significance improvement in mean change from baseline for higher rivastigmine treatment groups on LOCF analysis compared with placebo but not for higher dose rivastigmine on ITT analysis or lower dose rivastigmine on either type of analysis. The number of patients with improvement of ≥ 4 points was greater for higher rivastigmine dose compared with placebo on LOCF analysis only

- ITT analysis: mean (95% CI) change from baseline: higher dose rivastigmine, 0.26 (–0.66 to 1.06); lower dose rivastigmine, –1.37 (–2.27 to –0.53); placebo, –1.34 (–2.19 to –0.41). Higher dose rivastigmine vs placebo ($p < 0.1$); lower dose rivastigmine vs placebo ($p > 0.05$). Higher dose rivastigmine vs placebo (24% vs 16%; $p < 0.1$); lower dose rivastigmine vs placebo (15% vs 16%; $p > 0.05$)
- LOCF analysis: mean (95% CI) change from baseline: higher dose rivastigmine, 0.83 (–0.19 to 1.79); lower dose rivastigmine, –1.24 (–2.23 to –0.37); placebo, –1.45 (–2.33 to –0.47). Higher dose rivastigmine vs placebo ($p < 0.001$); lower dose rivastigmine vs placebo ($p > 0.05$). Patients with improvement of ≥ 4 points: higher dose rivastigmine vs placebo (27% vs 18%; $p < 0.05$); lower dose rivastigmine vs placebo (16% vs 18%; $p > 0.05$)

CIBIC-plus: statistically significance improvement in mean change from baseline for higher rivastigmine treatment groups on ITT and LOCF analysis compared with placebo but not for lower dose rivastigmine on either type of analysis. The number of patients with improvement of ≥ 4 points was greater for both rivastigmine doses on both types of analysis

- ITT analysis: mean (95% CI) change from baseline: higher dose rivastigmine, 3.91 (3.71 to 4.09); lower dose rivastigmine, 4.24 (4.02 to 4.38); placebo, 4.38 (4.22 to 4.58). Higher dose rivastigmine vs placebo ($p < 0.001$); lower dose rivastigmine vs placebo ($p > 0.05$). Patients with improvement (scores 1, 2, 3 points): higher dose rivastigmine, 37%; lower dose rivastigmine, 30%; placebo, 20%. Higher dose rivastigmine vs placebo ($p < 0.001$); lower dose rivastigmine vs placebo ($p > 0.05$)
- LOCF analysis: mean (95% CI) change from baseline: higher dose rivastigmine, 3.88 (3.69 to 4.11); lower dose rivastigmine, 4.17 (4.0 to 4.4); placebo, 4.32 (4.1 to 4.5). Higher dose rivastigmine vs placebo ($p < 0.001$); lower dose rivastigmine vs placebo ($p > 0.05$). Patients with improvement (scores 1, 2, 3 points): higher dose rivastigmine, 40%; lower dose rivastigmine, 32%; placebo, 22%. Higher dose rivastigmine vs placebo ($p < 0.001$); lower dose rivastigmine vs placebo ($p > 0.05$)

continued

contd
Rosler, *et al*., (1999)[48]

***Results* contd**

PDS: statistically significance improvement in mean change from baseline for higher rivastigmine treatment groups on LOCF analysis compared with placebo but not for lower dose rivastigmine on either type of analysis or for higher dose on ITT analysis

- ITT analysis: mean (95% CI) change from baseline: higher dose rivastigmine, 0.05 (–1.57, 1.77); lower dose rivastigmine, –3.37 (–4.99 to –1.61); placebo, –2.18 (–3.91 to –0.49). Higher dose rivastigmine vs placebo ($p < 0.1$); lower dose rivastigmine vs placebo ($p > 0.05$)
- LOCF analysis: mean (95% CI) change from baseline: higher dose rivastigmine, 0.5 (–1.32 to 2.52); lower dose rivastigmine, –3.31 (–5.1 to –1.5); placebo, –2.23 (–4.02 to –0.38). Higher dose rivastigmine vs placebo ($p < 0.05$); lower dose rivastigmine vs placebo ($p > 0.05$)

MMSE: statistically significant improvement in mean change from baseline for higher rivastigmine groups compared with placebo on ITT and LOCF analysis ($p < 0.05$ on both analyses). Significance of difference for lower dose vs placebo not reported

- ITT analysis: higher dose, 0.21 (–0.24 to 0.64); lower dose, –0.62 (–1.05 to –0.15); placebo, –0.47 (–0.96 to –0.04). Higher dose versus placebo ($p < 0.05$); lower dose versus placebo (p not stated)
- LOCF analysis: higher dose, 0.34 (–0.25 to 0.85); lower dose –0.60 (–1.08 to –0.12); placebo, –0.54 (–0.99 to –0.01). Higher dose versus placebo ($p < 0.05$); lower dose versus placebo (p not stated)

Global deterioration scale: statistically significant improvement in mean change from baseline for higher rivastigmine groups compared with placebo on ITT and LOCF analysis ($p < 0.05$ on both analyses). Significance of difference for lower dose vs placebo not reported

- ITT analysis: higher dose, –0.06 (–0.02 to 0.0); lower dose, –0.22 (–0.3 to –0.1); placebo, –0.26 (–0.4 to –0.2). Higher dose versus placebo ($p < 0.05$); lower dose versus placebo (p not stated)
- LOCF analysis: higher dose, –0.03 (–0.13 to 0.13); lower dose, –0.2 (–0.3 to –0.09); placebo, –0.24 (–0.31 to –0.09). Higher dose versus placebo ($p < 0.05$); lower dose versus placebo (p not stated)

Adverse effects:
Significantly more patients reported at least one adverse reaction in the higher dose group (91%) compared with the lower dose group (71%) or placebo (72%). The following adverse events were significantly more common in patients receiving higher dose rivastigmine compared with placebo (rates reported as higher dose; lower dose; placebo): nausea (50% vs 17% vs 10%); vomiting (34% vs 8% vs 6%); dizziness (20% vs 10% vs 7%); headache (19% vs 7% vs 8%); diarrhoea (17% vs 10% vs 9%); anorexia (14% vs 3% vs 2%); abdominal pain (12% vs 5% vs 3%); fatigue (10% vs 2% vs 3%) malaise (10% vs 1% vs 2%). Nausea was significantly more common in patients receiving lower dose rivastigmine than those receiving placebo. The incidence of serious adverse events was similar in all groups (18%). Proportions discontinuing treatment due to adverse events was significantly greater in the higher dose rivastigmine group compared with both the lower dose and placebo: higher dose, 23%; lower dose, 7%; placebo, 7%

Methodological comments

- Allocation to treatment groups: random, using computer generated allocation
- Comparability of treatment groups: treatment groups were reported as comparable at baseline on demographic and disease characteristics though limited data was presented (apart from age, ADAS-cog and PDS)
- Blinding: double-blind, using identical blinding capsules and comparable numbers of capsules
- Method of data-analysis: ADAS, CIBIC and PDS (categorical analysis) were analysed with ANOVA and Mantel–Haenszel blocking for centre. Results were reported for ITT analysis; LOCF analysis included randomised patient with at least one evaluation while being treated; and OC analysis including randomised patients with an evaluation made while on study drug at designated assessment time. Point estimates of differences between active treatment and placebo groups were not reported though p values for differences were reported
- Sample size/statistical power: sample size estimated at 200 per group to achieve power of 90% in detecting at least a 3-point improvement on ADAS and an increase from 15% to 30% among patients scoring < 4 on CIBIC
- Attrition/drop-out: reasons were given for withdrawals by treatment group

General comments

- The inclusion and exclusion criteria were clearly defined and participants included those with co-existing disease and on concomitant drug therapy
- Supported by funding from Novartis Pharma

continued

contd
Rosler, *et al*., (1999)[48]

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1 (computer generated)
Was the study described as double-blind?	1 + 1 (method of blinding described)
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 20% Rivastigmine (lower dose): 14% Rivastigime (higher dose): 32.5% Placebo: 13%

Note

Data summaries have been omitted for two unpublished studies (CIC data):

Novartis Pharmaceuticals 2000. ENA B304 (a multinational (Australia, Canada, Italy, Ireland, RSA, UK), multicentre (37 centres), randomised, double-blind, placebo-controlled, parallel-group trial)

Novartis Pharmaceuticals 2000. ENAB351 (a multicentre (14 centres) randomised, double-blind, placebo-controlled, parallel-group trial carried out in the USA. (Part published[74]))

Appendix 10

Summary of evidence of effectiveness of galantamine in AD

Reference and design	Intervention	Patients	Outcome measures
Wilcock, *et al*., 1997[49] UK *Study type/design*: RCT (Phase II) *Jadad score*: 1/5	*Treatment arms*: 1. Galantamine hydrobromide 22.5 mg/day 2. Galantamine hydrobromide 30 mg/day 3. Galantamine hydrobromide 45 mg/day 4. Placebo *Length of treatment*: 12 weeks (composed of 2-week wash-out period, with following dose escalation: day 1–2, 5 mg b.d.; increased at 2–3 day intervals until target dose achieved (5, 8 and 14 days respectively), with 10 weeks continuous fixed medications *Other interventions used*: not stated	*Number of patients*: Total: = 253 1. 22.5 mg: 83 2. 30 mg: 54 3. 45 mg: 54 Placebo: 62 *Characteristics of target population*: outpatients diagnosed with probable AD on NINCDS-ADRDA and DSM-III-R *Exclusion*: anti-nausea medication not permitted *Participants' characteristics*: not stated *Setting*: not stated	Outcomes assessed at baseline, 6 weeks and 12 weeks *Primary outcome*: ADAS-cog *Secondary outcomes*: CIBIC-plus IADL PDS-1 Adverse events Length of follow-up: 12 weeks

Results

ADAS-cog mean change from baseline score at 12 weeks (ITT): placebo, –2.5 (95% CI, –4.25 to –0.875; p = ns); 22.5 mg, –1 (95% CI, –2.75 to 0.75; p = ns); 30 mg, 0.875 (95% CI, –0.75 to 2.625; p = 0.008); 45 mg, –0.25 (95% CI, –2 to 1.5; p = ns) (figures estimated from graph)

Adverse events (proportion with adverse event):
Nausea: placebo, 0%; 22.5 mg, 13%; 30 mg, 18%; 45 mg, 35%
Vomiting: placebo, 6%; 22.5 mg, 19%; 30 mg, 7%; 45 mg, 17%

Methodological comments

- Allocation to treatment groups: random, method not stated
- Blinding: not stated, although all received three divided doses daily with food
- Comparability of treatment groups: no information provided
- Method of data-analysis: not stated
- Sample size/statistical power: 90% power to show a 4-point change on ADAS-cog between treatment and placebo
- Attrition/drop-out: withdrawals due to adverse effects – placebo, 8%, 22.5 mg/day, 22%, 30 mg/day, 16%, 45 mg/day, 38%

General comments

- Poorly reported Phase II trial
- Conflicts of interest: none stated

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	0 + 0
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Not stated

Reference and design	Intervention	Patients	Outcome measures
Tariot, *et al*., 2000[50] USA *Study type/design*: Multicentre, parallel group, placebo-controlled, double-blind RCT *Jadad score*: 5/5	*Treatment arms*: 1. Galantamine 8 mg/day 2. Galantamine 8 mg/day for 4 weeks, followed by 16 mg/day for 17 weeks 3. Galantamine 8 mg/day for 4 weeks, 16 mg/day for 4 weeks, followed by 24 mg/day for weeks 9 to 21 4. Placebo *Length of treatment*: 6 months (composed of 4 weeks single-blind run-in, 8-week dose titration phase) *Other interventions used*: other antidementia drugs had to be stopped before entry if licensed or 30 days if unlicensed. Drugs for concomitant diseases were permitted, except sedative-hypnotics or sedating cough/cold remedies 48 hours before assessment	*Number of patients*: Total: 978 1. Galantamine 8 mg: 140 2. Galantamine 16 mg: 279 3. Galantamine 24 mg: 273 4. Placebo: 286 *Characteristics of target population*: history of cognitive decline with gradual onset and progressive for 6 months; diagnosis of probable AD on NINCDS-ADRDA; MMSE score 10 to 22 and score of ≥ 18 on 11-item cognitive subscale of ADAS-cog. CT or MRI scan in last 12 months showing no signs of clinically significant multi-infarct dementia or active cerebrovascular disease. Patient had a responsible care-giver *Exclusion*: Although patients with controlled concomitant diseases such as hypertension, heart failure, type II diabetes mellitus or hypothyroidism were included, patients with other neurodegenerative disorders, cardiovascular disease thought to prevent completion of study, clinically significant psychiatric, hepatic, renal, pulmonary, metabolic or endocrine conditions, or urinary outflow obstruction, active peptic ulcer, history of epilepsy or significant drug or alcohol abuse were excluded. Patients taking a cholinomimetic agent in previous 60 days excluded *Participants' characteristics*: 36% men; age range 76.0 (± 0.4) to 77.7 (± 0.6) years; white race ranged 91% to 94%; other medical conditions ranged 96% to 98%; mean MMSE score ranged 17.7 (± 0.2) to 18.0 (± 0.3); mean ADAS-cog score ranged 27.8 (± 0.9) to 29.4 (± 0.6). Baseline demographic and medical characteristics were comparable between groups *Setting*: not specified	Outcomes assessed at baseline, 4 weeks, 13 weeks and 5 months *Primary outcomes*: ADAS-cog CIBIC plus *Secondary outcomes*: Proportion of responders (≥ 4 points on ADAS-cog relative to baseline) Proportion of improving ≥ 7 points on ADAS-cog 23-item AD Cooperative Study (ADCS) ADL inventory NPI *Safety and adverse event monitoring*: physical examinations electrocardiography vital signs standard laboratory tests adverse events Length of follow-up: 5 months

Results

ADAS-cog mean (SEM) change from baseline: placebo, +1.7 (0.39), n = 255; 8 mg, +0.4 (0.52), not significant vs placebo, n = 126; 16 mg, –1.4 (0.35), significant vs placebo $p < 0.001$, n = 253; 24 mg, –1.4 (0.39), significant vs placebo $p < 0.001$, n = 253

CIBIC-plus proportion of patients stable/improved: placebo, 49%; 8 mg, 53% (ns); 16 mg, 66% (significant vs placebo at $p < 0.001$); 24 mg, 64% (significant vs placebo $p < 0.001$)

ADCS/ADL: mean (SEM) change from baseline: placebo, –3.8 (0.6), n = 262; 8 mg, –3.2 (0.8), ns vs placebo, n = 129; 16 mg, –0.7 (0.5), significant vs placebo $p < 0.001$, n = 255; 24 mg, –1.5 (0.6), significant vs placebo, $p < 0.01$, n = 253

NPI mean (SEM) change from baseline: placebo, 2.0 (0.7), n = 262; 8 mg, 2.3 (1.0), ns vs placebo, n = 129; 16 mg –0.1 (0.7), significant vs placebo $p < 0.05$, n = 255; 24 mg, 0.0 (0.8), significant vs placebo $p < 0.05$, n = 253

continued

contd
Tariot, *et al*., 2000[50]

***Results* contd**
Adverse effects:
Withdrawals due to adverse events were overall 75/978 patients (8%); galantamine 8 mg, 9/140 patients (6%); galantamine 16 mg, 19/279 patients (7%); galantamine 24 mg, 27/273 patients (10%); placebo, 20/286 patients (7%)

Adverse events where 5% difference between placebo, and galantamine group: nausea (placebo, 4.5%: 8 mg, 5.7%: 16 mg, 13.3%: 24 mg, 16.5%), vomiting (placebo, 1.4%: 8 mg, 3.6%: 16 mg, 6.1%: 24 mg, 19.9%), anorexia (placebo, 3.1%: 8 mg, 5.7%: 16 mg, 6.5%: 24 mg, 8.8%), agitation (placebo, 9.4%: 8 mg, 15.0%: 16 mg, 10.0%: 24 mg, 8.1%), diarrhoea (placebo, 5.9%: 8 mg, 5.0%: 16 mg, 12.2%: 24 mg, 5.5%), any event (placebo, 72.0%: 8 mg, 75.7%: 16 mg, 73.8%: 24 mg, 80.2%), deaths (placebo, 1.4%: 8 mg, 0.7%: 16 mg, 1.1%: 24 mg, 1.1%)

Safety monitoring showed no significant differences between groups on any indicator

Methodological comments
- Allocation to treatment groups: random, computer-generated
- Blinding: double-blind using identical single tablets orally twice daily
- Comparability of treatment groups: thought comparable on baseline demographic and medical factors
- Method of data-analysis: Randomised patients receiving one dose were included in baseline characteristics and safety data. Efficacy used randomised patient available at assessment, as well as ITT analyses using LOCF. ANOVA for continuous variables and Cochran–Mantel–Haenszel test for categorical variables were used for baseline comparisons, with *t*-tests and ANCOVA for analysis of changes in scores. *A priori* hypotheses investigating effects of declining dose were specified
- Sample size/statistical power: not calculated for present study but uses previous study's calculation. To detect a mean difference of 3 points from baseline in ADAS-cog between placebo and either of 2 higher dose treatment groups with > 95% power (α = 0.05) would require 208 patients per group
- Attrition/drop-out: appropriately stated with reasons

General comments
- The inclusion criteria were clearly defined
- Secondary outcomes of proportion of responders (≥ 4 points on ADAS-cog relative to baseline) and proportion of improving ≥ 7 points on ADAS-cog were not reported in full for ITT and were excluded from data extraction
- Supported by Janssen Research Foundation

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 199/978 patients (20%) 1. Galantamine 8 mg: 32/140 patients (23%) 2. Galantamine 16 mg: 60/279 patients (22%) 3. Galantamine 24 mg: 61/273 patients (22%) 4. Placebo: 46/286 patients (16%)

Reference and design	Intervention	Patients	Outcome measures
Raskind, *et al*., 2000[51] USA *Study type/design*: Multicentre, parallel-group, placebo-controlled, double-blind trial *Jadad score*: 5/5	*Treatment arms*: 1.Galantamine 8 mg/day for 1 week, 16 mg/day for 1 week, 24 mg/day to study end 2. Galantamine 8 mg/day for 1 week, 16 mg/day for 1 week, 24 mg/day for 1 week, 32 mg/day to study end 3. Placebo *Extension phase*: 8 mg/day for 1 week, 16 mg/day for 1 week, 24 mg/day for 5.5 months *Length of treatment*: 6 months (composed of 4 weeks single-blind placebo run-in, 4-week dose titration phase) followed by a 6-month open label extension *Other interventions used*: other antidementia drugs had to be stopped before entry. Drugs for concomitant diseases were permitted, except sedative-hypnotics or sedating cough/cold remedies 48 hours before assessment	*Number of patients*: Total: 636 1. Galantamine 24 mg: 212 2. Galantamine 32 mg: 211 3. Placebo: 213 Extension phase: 353 *Characteristics of target population*: history of cognitive decline with gradual onset and progressive for 6 months; diagnosis of probable AD on NINCDS-ADRDA; probable dementia mild to moderate dementia MMSE score 11 to 24 and score of ≥ 12 on cognitive subscale of ADAS-cog. Patient had a responsible care-giver *Exclusion*: Although patients with controlled concomitant diseases such as hypertension, heart failure, non insulin dependent diabetes mellitus or hypothyroidism were included, patients with other neurodegenerative disorders, cardiovascular disease thought to prevent completion of study, clinically significant cerebrovascular disease, psychiatric, hepatic, renal, pulmonary, metabolic or endocrine conditions, or urinary outflow obstruction, active peptic ulcer, history of epilepsy or significant drug or alcohol abuse were excluded. Patients taking a cholinomimetic agent in previous 3 months excluded *Participants' characteristics*: 38% men; age range 75.0 (± 0.6) to 75.9 (± 0.5); white race ranged 90% to 92%; other medical conditions ranged 91.9% to 95.3%; mean MMSE score ranged 19.1 (± 0.3) to 19.5 (± 0.3); mean ADAS-cog score ranged 24.8 (± 0.7) to 25.8 (± 0.8); mean DAD score ranged 70.3 (± 1.6) to 71.1 (± 1.5). Baseline demographic and medical characteristics were comparable between groups, except time since diagnosis ranged 1.02 (± 0.10) to 1.45 (± 0.13) ($p = 0.02$) *Setting*: not specified	Outcomes assessed at baseline (first visit in 6 month phase), 3 months and 6 months. Extension phase at 3 and 6 months *Primary outcomes*: ADAS-cog (11 item) CIBIC plus *Secondary outcomes*: ADAS-cog (13 item) Proportion of responders (≥ 4 points on ADAS-cog relative to baseline) ADL inventory assessed using DAD scale *Safety and adverse event monitoring*: physical examinations electrocardiography vital signs standard laboratory tests Adverse events Length of follow-up: 6 months of treatment and 6 months of extension

Results

ADAS-cog mean (SEM) change from baseline: placebo, +2.0 (0.45), $n = 207$; 24 mg, –1.9 (0.36), vs placebo $p < 0.001$, $n = 202$; 32 mg/day, –1.4 (0.44), vs placebo $p < 0.001$, $n = 197$

CIBIC-plus score: (1 = Markedly improved; 2 = Moderately improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worsened; 6 = Moderately worsened; 7 = Markedly worsened) – proportion by score:

- Placebo: 1 = 0.5; 2 = 3.6; 3 = 9.7; 4 = 42.9; 5 = 30.6; 6 = 12.2; 7 = 0.5
- 24 mg: 1 = 1.6; 2 = 3.2; 3 = 15.1; 4 = 53.2; 5 = 19.4; 6 = 5.4; 7 = 2.2 (vs placebo $p < 0.01$)
- 32 mg: 1 = 1.2; 2 = 2.3; 3 = 12.3; 4 = 53.2; 5 = 25.1; 6 = 5.3; 7 = 0.6 (vs placebo $p < 0.05$)

ADAS-cog (11 item) responders (≥ 4 points on ADAS-cog relative to baseline): placebo, 16.6%, 24 mg, 33.3% (vs placebo $p < 0.01$), 32 mg, 33.6% (vs placebo $p < 0.01$)

ADAS-cog (13 item): 24 mg and 32 mg had significant advantage over placebo ($p < 0.01$), no data provided

ADL inventory assessed using DAD scale: no significant difference in mean change in total DAD score

continued

contd
Raskind, *et al.*, 2000[51]

***Results* contd**
Adverse effects:
Withdrawals due to adverse events were overall 132/636 patients (21%); galantamine 24 mg, 49/212 patients (23%); galantamine 32 mg, 67/211 patients (32%); placebo, 16/213 patients (8%)

Adverse events where 5% difference between placebo, and galantamine group: nausea (placebo, 13.1%; 24 mg, 37.3%; 32 mg, 43.6%), vomiting (placebo, 7.5%; 24 mg, 20.8%; 32 mg, 25.6%), anorexia (placebo, 5.6%; 24 mg, 13.7%; 32 mg, 20.4%), dizziness (placebo, 11.3%; 24 mg, 13.7%; 32 mg, 18.5%), diarrhoea (placebo, 9.9%; 24 mg, 12.3%; 32 mg, 19.4%), weight loss (placebo, 4.7%; 24 mg, 12.3%; 32 mg, 10.9%), abdominal pain (placebo, 4.2%; 24 mg, 6.6%; 32 mg, 10.9%), tremor (placebo, 0.5%; 24 mg, 5.2%; 32 mg, 3.3%), any adverse event (placebo, 78.9%; 24 mg, 92.0%; 32 mg, 92.4%)

Safety monitoring showed no significant differences between groups on any indicator

Methodological comments
- Allocation to treatment groups: random, computer-generated
- Blinding: double-blind using identical single tablets twice daily
- Comparability of treatment groups: considered comparable on baseline demographic and medical characteristics
- Method of data-analysis: randomised patients receiving one dose were included in baseline characteristics and safety data. Efficacy used randomised patients providing post-baseline data available at assessment, as well as ITT analyses using LOCF. ANOVA for continuous variables and Cochran–Mantel–Haenszel test for categorical variables were used for baseline comparisons, ANCOVA for analysis of changes in scores. Time–response relationships for change were analysed through generalised interactive modelling. Results were extracted for ITT using LOCF. Although more conservative than OC, LOCF analyses are liable to inflate effects where there are large numbers of withdrawals, as in the present study
- Sample size/statistical power: not calculated for present study but uses previous studies calculation. To detect a mean difference of 2.75 points from baseline in ADAS-cog between placebo and galantamine group with 80% power (α = 0.025 with Bonferroni adjustment) would require 125 patients per group
- Attrition/drop-out: appropriately stated with reasons

General comments
- The inclusion criteria were clearly defined
- Secondary outcomes of proportion of responders (≥ 4 points on ADAS-cog relative to baseline), ADAS-cog (13 item) and ADL inventory assessed using DAD scale were not reported in full for ITT
- Outcomes for the 6 month open label extension are not examined as the characteristics of the patients are not discussed and results are not reported in full
- Supported by Janssen Research Foundation

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1 + 1
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 198/636 patients (31%) 1. Galantamine 24 mg: 68/212 patients (32%) 2. Galantamine 32 mg: 89/211 patients (42%) 3. Placebo: 41/213 patients (19%)

Note

Data summaries have been omitted for three unpublished studies (CIC data):

Wilcock, et al. *(multicentre, randomised, double-blind, parallel-group, placebo-controlled trial carried out in Canada, Finland, France, Germany, Norway, Sweden, The Netherlands and the UK)*

Rockwood, et al. *(multicentre, randomised, parallel-group, placebo-controlled, double-blind trial carried out in USA, Canada, GB, South Africa, Australia, NZ)*

Wilkinson, et al. *(randomised, parallel-group, placebo-controlled, double-blind trial (Phase II) carried out in the UK)*

Appendix 11

Economic evaluations of donepezil and rivastigmine

TABLE 13 *Internal validity of donepezil studies*

Item	Study 1 (Stein, 1997[25])	Study 2 (Stewart, *et al.*, 1998[54])	Study 3 (Jonsson, *et al.*, 1999[55])	Study 4 (O'Brien, *et al.*, 1999[56])	Study 5 (Neumann, *et al.*, 1999[57])
1. Well-defined question	✔ Included late in review process – only single person assessment for quality and data extraction	✔	✔	✔	✔
2. Clear description alternatives	Rivastigmine not option (not licensed then in UK)	✔ Tacrine and rivastigmine not options (not licensed then in UK)	Not clear why tacrine or rivastigmine not options	✔ Tacrine and rivastigmine not options (not licensed or launched in Canada, respectively)	Not clear why tacrine not an option. Rivastigmine not an option (not launched)
3. Reasonable study type	?	✔	✔	✔	✔
4. Effectiveness established	Potentially 3 phase III RCTs (A301 (unpublished at the time of the economic evaluation), A302[75] (Jadad score, 2/5), A202[76] (details of study unknown) and one Phase II RCT[38] (Jadad score, 4/5). Treatment delayed progression by 3–6 months	1 good quality RCT (Jadad score 5/5) = Rogers, *et al.* (1998) 30 weeks[39]	1 good quality RCT (Jadad score 5/5) = Rogers, *et al.* (1998) 30 weeks[39]	1 good quality RCT (Jadad score 5/5) = Rogers, *et al.* (1998) 30 weeks[39]	1 good quality RCT (Jadad score 5/5) = Rogers, *et al.* (1998) 30 weeks[39]
5. Estimates related to population risks	Unclear how effectiveness data and QALYs were linked in the calculations. Some non-drug treatment costs identified and valued, but not used in CUA Source of resource use for non-drug treatment costs (outpatient visits and CT scans) not stated (may have been assumption)	Sub-group analysis for mild and moderate groups (MMSE 15–20 and 10–14 respectively, by dose of donepezil) 1. Refined analyses of Cambridge cohort **of elderly patients** (> 75 years, but ? collection period) for disease progression of untreated patients 2. Mortality data from two studies (? population and collection period). 3-year death rate annualised and extrapolated to 5 years 3. Resource use from analysis of 2 OPCS surveys (1985–86) in Great Britain for sub-sample with **advanced cognitive impairment**. Costing by mapping OPCS SEVINT to MMSE. Limited information on service use. Required many other data sources Potentially progression and resource use data from a different population to that of the RCT	No sub-group analysis although MMSE used so presumably raw data could generate sub-group analyses Kungsholmen Project longitudinal study of health status and resource use (1987/89 and 1991/92). Then selected out patients with **dementia** (n = 206). Patients were ≥ 75 years old (mean 84.5 years) compared with mean 72.6–74.6 years in RCT[39]	Sub-group analyses available for MMSE 10–14, 15–20, and 21–26 Refined analyses of: 1. Alberta clinic patients (cohort, n = 243) with AD (distribution of MMSE scores and mortality data), dates of data collection unknown 2. Canadian Study of Health & Ageing (CSHA, cross sectional study)[77] – across 18 centres, 2 years, ≥ 65 years, 1991–92, to identify AD patients and costing from resource use data also collected Not possible to assess comparability of RCT and cohort/cross sectional study patients	Sub-group analysis by mild/community and moderate/community at start, (**CDR scores**) 1. Underlying disease progression from longitudinal database of patients with **dementia** (n = 1145, CERAD, 1986–95) 2. Cost estimates from small study[78] of AD patients (n = 187) in community and institutional settings in California. Not random sample, only one geographic area and ? method of classifying disease severity (data collection 1988–90). Not possible to assess comparability of RCT and other study patients (progression, cost and QALYs (see below))

continued

TABLE 13 contd *Internal validity of donepezil studies*

Item	Study 1 (Stein, 1997[25])	Study 2 (Stewart, *et al.*, 1998[54])	Study 3 (Jonsson, *et al.*, 1999[55])	Study 4 (O'Brien, *et al.*, 1999[56])	Study 5 (Neumann, *et al.*, 1999[57])
6. Relevant costs and consequences identified	(✔) Healthcare resources (drug costs only), ✔ adverse events (not quantified) X Patient/family resources X Social care sector resources ✔ Patient benefits X Carer benefits	✔ Healthcare resources, but ? adverse events ✔ Patient/family resources ✔ Social care sector resources ✔ Patient benefits X Carer benefits	✔ Healthcare resources, but ? adverse events X Patient/family resources ✔ Social care sector resources ✔ Patient benefits X Carer benefits	✔ Healthcare resources, but ? adverse events ✔ Patient/family resources ✔ Social care sector resources ✔ Patient benefits X Carer benefits	✔ Healthcare resources, ? adverse events (although drop-out rate considered) ✔ Patient/family resources ✔ Social care sector resources ✔ Patient benefits (proxy HUI) (✔) Carer benefits
7. Costs and consequences measured accurately	? Source of drug costs not stated QALYs estimated (? by one person) based on the IHQL (Index of Health Related Quality of Life) index which is not well validated	? (Resource use measured by interview (survey of patients +/– carers)). However, insufficient detail in 'costs paper'[67] (refers to further papers), and the authors advise caution. Incomplete valuation of some costs (e.g. informal carers) Number of years in non-severe state (i.e. MMSE ≥ 10) over 5 years using current mortality data and RCT effect rolled out	✔ (Resource use measured by interviewing patients and family members) Number of years in non-severe state (i.e. MMSE ≥ 10) over 5 years using current mortality data and RCT effect rolled out	✔ (Resource use measured based on CSHA interview data) Number of years in non-severe state (i.e. MMSE ≥ 10) over 5.06 years using current mortality data and RCT effect rolled out	? (Resource use based on interview and care-giver calendars (prospective) over 12 months). However, full details of costing methods (e.g. social services) not given in costs paper[78] QALYs based on care-giver proxy from cross-sectional study, but HUI:2 not validated in AD. Mean age varied (range by severity 77–84 years). Effect duration from experts, drop-out rate 4% every 6-week cycle (from open label study)
8. Costs and consequences valued credibly	Excluded drug acquisition costs (e.g. dispensing). Unit costs for non-drug treatment based on ECRs for one region that were often over-inflated (but by unknown percentage) and are now obsolete. ? year ? 1996/97 for clinic but ? for CT scans	Unclear whether: 1. Donepezil costs (1997) deflated to 1996, although this may not matter as drug costs often do not increase in the UK (donepezil costs static 1997–2000) 2. What drug acquisition costs included (e.g. source, dispensing, pharmacy mark-up for donepezil) Some databases and sources of information for costs/resource use reflect service arrangements in mid-1980s	Unclear whether: 1. Cost data[79] re-analysed for patients with dementia and MMSE states in economics paper[55] 2. Drug dispensing costs and pharmacy mark-up were included. (Intervention costs excluded extra physician visits, additional laboratory tests, etc.) 3. Interpretation. Base case presented undiscounted costs, whereas sensitivity analyses used only discounted costs	Service use from CSHA combined with local volumes and charges in Hamilton.[80] Justified exclusion of acute hospital care costs. Variety of sources used, some of which were based on people with dementia (not AD) or expert opinion	Average wholesale price for donepezil. Formal care costs from billing data (1990 inflated). Experts estimated additional visits to doctor for donepezil Assumed that costs for moderate AD patients were midway between mild and severe, but only 5 people with mild/mod dementia in an institution Care-giver mapping patients' health states to HUI values (but ? only for Canadian use)

continued

TABLE 13 contd *Internal validity of donepezil studies*

Item	Study 1 (Stein, 1997[25])	Study 2 (Stewart, *et al.*, 1998[54])	Study 3 (Jonsson, *et al.*, 1999[55])	Study 4 (O'Brien, *et al.*, 1999[56])	Study 5 (Neumann, *et al.*, 1999[57])
9. Differential timing considered	✔ (6% for costs, no justification given, although accepted UK rate. No benefit assumed beyond 1 year)	✔ (6% for costs based on HM Treasury guidelines)	✔ (3% for costs only, however no justification given and the costs paper[79] used 5%)	✔ (5% for costs and benefits, based on Ontario Ministry of Health guidelines)	✔ (3% for costs and benefits, no justification given)
10. Incremental analysis performed	✔	✔	✔	✔	✔
11. Sensitivity analysis performed	✔ Two three-way	✔ One-way on 2 variables	✔ One-way on 3 variables	✔ One-way on 8 variables	✔ One-way and threshold on 8 variables
12. Modelling conducted reasonably	✗ (Very simplistic)	? Bias	? Bias	? Bias	? Bias

? means unclear or unknown

✔ means item included or judged to have acceptable internal validity

✗ means factor not included or judged to have unacceptable internal validity

ECR, extra contractural referral; HUI, Health Utilities Index (versions II or III)

TABLE 14 *Internal validity of rivastigmine studies*

Item	Study 6 (Stein, 1998[58])	Study 7 (Fenn & Gray, 1999[59])	Study 8 (Hauber, *et al.*, 2000[60])	Study 9 (Hauber, *et al.*, 2000[61])
1. Well-defined question	✔ Included late in review process therefore only underwent assessment for quality and data extraction by one person	✔	✔ Paper not indexed on the electronic databases at the time of initial searching – identified late and related papers could not be followed up. Paper only underwent assessment for quality and data extraction by one person	✔ Paper not indexed on the electronic databases at the time of initial searching – identified late and related papers could not be followed up. Paper only underwent assessment for quality and data extraction by one person
2. Clear description alternatives	Not clear why donepezil not included as an option	Not clear why donepezil not an option	Not clear why tacrine and donepezil not included as options	Did not consider alternative treatments, although gave justification
3. Reasonable study type	?	✔ Use of individual patient data is good practice; however, extrapolation beyond the 6 months efficacy data from the RCT still required	✔ As for Study 7	✔ As for Study 7
4. Effectiveness established	ADENA programme of 4 RCTs (study numbers B351, B352, B303 and B304). These appeared to be unpublished at the time of the economic evaluation[58] and details of study design, etc. were inadequate ? subsequent publication of these trials Treatment delayed progression by 6 months – assumed to be the same as for donepezil[25] (? evidence for this)	2 good quality RCTs (both Jadad scores 5/5) = Corey-Bloom, *et al.* (1998)[46] and Rosler, *et al.* (1999),[48] both 26 weeks	As for Study 7	As for Study 7
5. Estimates related to population risks	Unclear how effectiveness data and QALYs were linked in the calculations Source of resource use for non-drug treatment costs (outpatient visits and CT scans) not stated (? assumption)	Sub-group analysis for mild and moderate groups (MMSE 21–30 and 11–20, respectively) at **high dose** rivastigmine Results relate to trial population Likelihood of institutional care by severity from survey of patients in long-term care and distribution of non-institutionalised patients from RCT then combined with unit costs of care used to produce weighted estimates of annual care costs by severity	Results relate to trial population Used same model as Study 7[59] Likelihood of institutional care estimated from regression analysis of data from Consortium to Establish a Registry for AD (CERAD) and MMSE. No details given of patient characteristics	Results relate to trial population Used same model as Study 7[59] Resource use from Canadian Study of Health & Ageing (CSHA, cross sectional study)[77] – across 18 centres, 2 years, ≥ 65 years, 1991–92, to identify AD patients and costing from resource use data also collected. Not possible to assess comparability of RCT and cohort/cross sectional study patients Likelihood of institutionalisation based on CSHA[80]

continued

TABLE 14 contd *Internal validity of rivastigmine studies*

Item	Study 6 (Stein, 1998[58])	Study 7 (Fenn & Gray, 1999[59])	Study 8 (Hauber, *et al.*, 2000[60])	Study 9 (Hauber, *et al.*, 2000[61])
6. Relevant costs and consequences identified	(✔) Healthcare resources (drug costs only), ✔ adverse events (not quantified) X Patient/family resources X Social care sector resources ✔ Patient benefits (estimated IHQL) X Carer benefits	✔ Healthcare resources, but ? adverse events X Patient/family resources ✔ Social care sector resources ✔ Patient benefits X Carer benefits	✔ Healthcare resources, but ? adverse events ? Patient/family resources ? Social care sector resources ✔ Patient benefits X Carer benefits	✔ Healthcare resources, but ? adverse events ✔ Patient/family resources ✔ Social care sector resources ✔ Patient benefits (✔) Carer benefits – threshold analysis
7. Costs and consequences measured accurately	? Source of drug costs not stated QALYs estimated (? by one person) based on the IHQL (Index of Health Related Quality of Life) index which is not well validated	Costs based on home and institutional care costs from burden of illness paper[81] at 1990/91 prices Consequences in terms of days at MMSE > 10 aggregated for trial population groups	? Costs paper[62] not appraised Consequences in terms of average number of days saved by each baseline cohort delay in progression to more severe stages (by MMSE)	Resource use measured based on CSHA interview data Drug costs for rivastigmine on Canada unknown at time of evaluation – expected cost included in one analysis Consequences in terms of days saved by each (and all) baseline cohort delay in progression to more severe stages (by MMSE)
8. Costs and consequences valued credibly	Excluded drug acquisition costs (e.g. dispensing). Unit costs for non-drug treatment based on ECRs for one region that were often over-inflated (but by unknown percentage) and are now obsolete. ? year ? 1996/97 for clinic but ? for CT scans	Extrapolation beyond the trial unclear – varied between 2 and 4 years Excluded costs of rivastigmine, day hospital care, community nursing and informal carers Costs by age groups (for England) based on relatively old data (e.g. 1976–85, although often the most recent available) that may not reflect current budgetary distribution of resource use. In addition, derivation of costs required many assumptions regarding apportionment of dementia/other-related resource use to AD	Extrapolated beyond RCTs from 6 months to 2 years – assuming continuing effectiveness	Extrapolated beyond RCTs from 6 months to 2 years – assuming continuing effectiveness Service use from CSHA combined with local volumes and charges in Hamilton.[80] Justified exclusion of acute hospital care costs. Variety of sources used, some of which were based on people with dementia (not AD) or expert opinion Assumed monitoring costs and additional visits to physician negligible
9. Differential timing considered	✔ (6% for costs, no justification given, although accepted UK rate. Benefits not discounted – but no benefit assumed beyond 1 year)	X	✔ (3% for costs, however no justification given)	✔ (3% for costs, however no justification given)

continued

TABLE 14 contd *Internal validity of rivastigmine studies*

Item	Study 6 (Stein, 1998[58])	Study 7 (Fenn & Gray, 1999[59])	Study 8 (Hauber, *et al.*, 2000[60])	Study 9 (Hauber, *et al.*, 2000[61])
10. Incremental analysis performed	✔	✔	✔ Results presented separately for costs and effects. Effectiveness results not aggregated for study population or applied to local population – therefore overall average effectiveness not available	✔
11. Sensitivity analysis performed	✔ Two-way (2 variables) and one three-way analysis	X	X	X
12. Modelling conducted reasonably	✗ (Very simplistic)	? Bias ? Life expectancy incorporated in extrapolation beyond trial	? Bias Life expectancy not incorporated in extrapolation beyond trial	? Bias

? means unclear or unknown

✔ means item included or judged to have acceptable internal validity

✗ means factor not included or judged to have unacceptable internal validity

Note

CIC data on economic evlauations omitted

TABLE 15 *External validity of donepezil and rivastigmine studies*

	Study								
	Donepezil					Rivastigmine			
Item	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Patient group – are the patients in the study similar to those of interest in England and Wales?	? 2 studies in USA,[75,38] other 2 unknown therefore cannot ascertain whether patients similar to those in England and Wales ? Lower uptake rate of treatment	? Lower uptake rate of treatment likely to dilute effect and efficacy data from RCT in the USA	?	?	?	? Only one of the 4 RCTs included UK patients ? Lower uptake rate of treatment	? Lower uptake rate of treatment likely to dilute effect and efficacy data from RCTs in Europe, Canada and the USA	? As for Study 7	? As for Study 7
2. Healthcare system/setting – comparability of available alternatives? similar levels of resources? no untoward supply constraints? institutional arrangements comparable?	✔ But extremely narrow focus (drug costs only). Excluded any possible effect on long-term care. Unclear what impact delivery of therapy would have on costs	✔ Although possibly out of date as key issues are i) use of long-term accommodation, ii) how to deliver donepezil therapy (incl. follow-up care)	X	X	X	✔ But extremely narrow focus (i.e. principally drug costs only) that excluded any possible effect on long-term care. Unclear what impact delivery of therapy would have on costs	✔ As for Study 2	X	X
3. Treatment – comparability with clinical management?	? As for Study 2	? Is it important to manage adverse events	?	?	?	? As for Study 2	? As for Study 2	?	?
4. Resource costs – comparability between study and setting/population of interest?	Only drug costs used in analysis	? Full details costs used requires tracing a succession of papers. Unclear how local is resource use and whether this matters	X	X	X	? Non-drug costs were for crude costs from one UK region that may not reflect those nationally or the actual costs for people with AD	? Costs were crude national averages that may not reflect actual costs for people with AD	X	X
5. Marginal versus average costs – what difference does this make? Are there real cost savings from averting short periods in long stay care?	? Narrow focus of costs makes this difficult to assess	✔ Average costs to assess a national policy, but depends if assessment of local cost impact required	X	X	X	? Narrow focus of costs makes this difficult to assess	✔ As for Study 2	X	X

? means unclear or unknown

✔ means judged item suitable to generalise to England and Wales with or without some re-adjustment

X means factor judged not suitable as either not possible to see how an adjustment could be made easily in short/medium term or relevant data unavailable

Appendix 12

Clinical effectiveness studies reported as abstracts or conference presentations

Abstracts

Anand R, Hartman R, Gharabawi G. Worldwide clinical experience with Exelon, a new generation cholinesterase inhibitor, in the treatment of Alzheimer's disease (Abstract). *Eur J Neurol* 1997;**4**(Suppl 1):S37.

Cummings J, Anand R, Koumaras B, Hartman R. Rivastigmine provides behavioural benefits to Alzheimer's disease patients residing in a nursing home: findings from a 26-week trial. *Neurology* 2000;**54**(3):A468.

Cummings JL, Katz IR, Tariot P, Perdomo CA, Whalen E, Schwam EM, *et al.* Donepezil in the treatment of Alzheimer's disease in a nursing home population. *Neurology* 1999;**52**(2):A181.

Cutler NR, Veroff AE, Anand R, Hartman R, Mancione L. Correlation between cognitive effects and level of acetylcholinesterase inhibition in a trial of rivastigmine in Alzheimer patients. *Neurology* 1999;**52**(6):A173.

Doody RS, Pratt RD, Perdomo CA. Clinical benefits of donepezil: results from a long-term phase III extension trial. *Neurology* 1999;**52**(6):A174.

Farlow M, Hake AM, Wach J, Anand R. The response of patients with Alzheimer's disease to rivastigmine treatment is predicted by the rate of disease progression. *Neurology* 2000;**54**(3):A469.

Feidman H, Gauthier S, Hecker J, Vellas B, Whalen E. Benefits of donepezil on global function, behavior, cognition, ADLs in patients with moderate to severe Alzheimer's disease. *Neurology* 2000;**54**(3):A469.

Friedhoff L, Rogers SL. Donepezil lengthens time to loss of activities of daily living in patients with mild to moderate Alzheimer's disease – results of a preliminary evaluation. *Neurology* 1997;**48**(3):A100.

Friedhoff LT, Rogers SL. Donepezil maintains activities of daily living in patients with mild to moderately severe Alzheimer's disease: results of a retrospective analysis [abstract]. *Eur J Neurol* 1997;**4**(Suppl 1):S9.

Ivanoiu A, Vanderlinden M, Seron X, Maloteaux J-M, Sindic CJM. The effect of donepezil on memory and attention tests in Alzheimer's disease. *Neurology* 1999;**52**(2):A482.

Kewitz H, Berzewski H, Rainer M, Dal Bianco P, Friedl E, Deisenhammer E, *et al.* Galanthamine, a selective nontoxic acetylcholinesterase inhibitor is significantly superior over placebo in the treatment of SDAT. *Neuropsychopharmacology* 2000;**10**(35):130S.

Mohs R, Doody R, Morris J, Ieni J, Pratt R, Rogers S. Donepezil preserves activities of daily living in Alzheimer's disease patients: results from a one-year placebo-controlled functional survival study. *Neurology* 2000;**54**(3):A415.

Pratt R, Geldmacher D, Perdomo C. An evaluation of the long term efficacy of donepezil in patients from a Phase III clinical extension trial. *Neurology* 1999;**52**(2):A181.

Pratt RD, Geldmacher D, Perdomo CA. An evaluation of the long-term efficacy of donepezil in patients from a Phase III clinical extension trial. *Neurology* 1999;**52**(6):A481–A482.

Rainer M, Janoch P, Reiss AA. Galanthamine treatment in Alzheimer's disease: a preliminary evaluation of forty patients [abstract). *Can J Neurol Sci* 1993;**20**(Suppl 4):12.

Raskin M, Peskind E, Parys W, Wessel T. Galantamine produces long-term cognitive and functional benefits in patients with Alzheimer's disease. *Neurology* 2000;**54**(3):A468.

Rogers SL, Doody R, Mohs R, Friedhoff LT. E2020 produces both clinical global and cognitive test improvement in patients with mild to moderately severe Alzheimer's disease: results of a 30-week phase III trial. *Neurology* 1996;**46**(2):A217 S14.001.

Rogers SL, Friedhoff LT. E2020 improves cognition and quality of life in patients with mild-to moderate Alzheimer's disease: results of a phase-II trial. *Neurology* 1994;**44**(4 Suppl 2):A165.

Rogers SL, Friedhoff LT. Donepezil provides long-term clinical benefits for patients with Alzheimer's disease (AD). *J Neurol Sci* 1997;**150**(Suppl):S296.

Tariot P, Parys W, Kershaw P. The efficacy and tolerability of galantamine in Alzheimer's disease: a 5-month placebo-controlled study with slow dose escalation. *Neurology* 2000;**54**(3):A415.

Waldemar G, Winblad B, Engedal K, Soininen H, Verhey F, Wimo A, *et al.* Donepezil benefits patients with either mild or moderate Alzheimer's disease over one year. *Neurology* 2000;**54**(3):A470.

Wilcock G, Wilkinson D. Galanthamine hydrobromide: interim results of a group comparative, placebo controlled study of efficacy and safety in patients with a diagnosis of senile dementia of the Alzheimer type. *Neurobiol Aging* 1996;**17**(Suppl 4s):S144.

Winblad B, Engedal K, Solninen H, Verhey F, Waldemar G, Wimo A, *et al.* Donepezil slows deterioration in activities of daily living and improves the quality of life of patients with mild to moderate Alzheimer's disease over one year: results of a multinational double blind, placebo-controlled study. Quality of Life Evaluation of the Drug Informatics Association, 2000.

Conference presentations

Anand R, Hartman R, Messina J. New results with Exelon in the treatment of Alzheimer's disease. 5th Geneva/Springfield Symposium on Advances in Alzheimer Therapy; 1998.

Berzewski H. Galantamine, a selective nontoxic centrally acting and reversible acetylcholinesterase inhibitor for the treatments of SDAT. XIXth College of International Neuropsychopharmacologists Congress; 1994 June 27–July; Washington, DC.

Friedhoff LT, Farlow MR, Mohs RC, Rogers SL. Donepezil (E2020) demonstrates significant improvements in cognitive and global function in mild to moderately severe Alzheimer's disease (abstract). American College of Neuropsychopharmacology; 1996; San Juan, Puerto Rico.

Gauthier S, Rossor M, Hecker J, Burns A, Petite H, Moller H-J, *et al.* Results from a multinational phase III clinical trial of donepezil in Alzheimer's disease. Abstract for the Springfield Symposium; Geneva; 1998.

Gauthier S, Rossor M, Hecker J, Petit H, Mollet H-J, Mohr E, *et al.* Donepezil produces clinical, global and cognitive test improvements in patients with Alzheimer's disease: results of the 30-week multinational donepezil study. Presented at the 6th International Stockholm/ Springfield Symposium on Advances in Alzheimer Therapy; 2000 5–8 April.

Gauthier S, *et al.* Donepezil improves neuropsychiatric symptoms in moderate to severe Alzheimer's disease. Presented at the Annual Meeting of the American Psychiatric Association; 2000 13–18 May.

Kewitz H, Davis B. Preclinical and clinical studies on galanthamine for Alzheimer's disease treatment. 39. 3rd International Springfield Symposium on Advances in Alzheimer Therapy; 1994.

Mintzer J, Wessel T. Galantamine produces long-term cognitive and functional benefits in patients with Alzheimer's disease. Poster presented at the 7th International World Alzheimer Congress; 2000; Washington, DC.

Mohs R, Doody R, Morris J, Ieni J, Rogers S, Perdomo C, *et al.* Donepezil preserves functional status in Alzheimer's disease patients: results from a 1-year prospective placebo-controlled study. 12th European College of Neuropsychopharmacology Congress; 1999.

Rainer M, Mucke H. Long term efficacy of galanthamine in Alzheimer's disease: cognitive parameters after two and three years of treatment. 8th Congress Association of European Psychiatrists; 1996; London.

Raskind M, Peskind E, Parys W, Wessel T. Galantamine produces long-term cognitive and functional benefits in patients with Alzheimer's disease. Presented at the 6th International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy; 2000 5–8 April.

Rockwood K. Kershaw P. Galantamine's clinical benefits are not offset by sleep disturbance: a 3 month placebo-controlled study in patients with Alzheimer's disease. Poster presented at the 7th International World Alzheimer Congress; 2000; Washington, DC.

Rogers SL, Friedhoff LT. Donepezil provides long-term clinical benefits for patients with Alzheimer's disease (AD). 16th World Congress of Neurology; 1997; Buenos Aires, Argentina.

Tariot P, Kershaw P, Yuan W. Galantamine postpones the emergence of behavioral symptoms in Alzheimer's disease: a 5-month, randomised, placebo-controlled study. Poster presented at the 7th International World Alzheimer Congress; 2000; Washington, DC.

Tariot P, Parys W, Kershaw P. The tolerability of galantamine in Alzheimer's disease: a 5-month placebo-controlled study with slow dose escalation. Poster presented at the 6th International Stockholm/ Springfield Symposium on Advances in Alzheimer Therapy; 2000 5–8 April.

Torfs K, Feldman H. 12-Month decline in cognitive and daily function in patients with mild-to moderate Alzheimer's disease treated with placebo in two randomized studies. Poster presented at the 7th International World Alzheimer Congress; 2000; Washington, DC.

Wilcock G, Lilienfeld S, Kershaw P. Galanthamine produces cognitive, functional and global benefits in patients with Alzheimer's disease: pooled data from two sixth month studies. Presented at the 6th International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy; 2000 5–8 April.

Wilcock G, Lilienfeld S. Galantamine alleviates caregiver burden in Alzheimer's disease: a 6-month placebo-controlled study. Poster presented at the 7th International World Alzheimer Congress; 2000; Washington, DC.

Wilkinson D, Lilienfeld S, and Truyen L. Galanthamine improves activities of daily living in patients with Alzheimer's disease: a 3 month, placebo-controlled study. Presented at the 6th International Stockholm/ Springfield Symposium on Advances in Alzheimer Therapy; 2000 5–8 April.

Winblad B, Engedal K, Solninen H, Verhey F, Waldemar G, Wimo A, *et al.* Donepezil slows deterioration in activities of daily living and improves the quality of life of patients with mild or moderate Alzheimer's disease over one year: results of a multinational double blind, placebo-controlled study. Poster presentation at the Quality of Life Evaluation of the Drug Informatics Association; 2000.

Appendix 13

Studies excluded from the review

Alzheimer's disease: investigational agents show promising results. *Geriatrics* 1996;**51**(9):15–6. [Non-RCT]

Treatment of Alzheimer's disease. *NZ Med J* 1997;**110**(1048):266. [Discussion document]

Donepezil for Alzheimer's disease? *Drug Ther Bull* 1997;**35**(10):75–6. [Non-systematic review]

New acetylcholinesterase inhibitor shows promise in largest Alzheimer's trial to date. *Formulary* 1997;**32**(12):1208. [Non-RCT)

Donepezil: new treatment for Alzheimer disease. *Who Drug Inf* 1997;**11**(1):20. [Non-systematic review]

Donepezil: a step forward compared with tacrine for Alzheimer's disease? *Drugs Ther Perspect* 1998;**11**(3):6–8. [Discussion document]

Admission of rivastigmine to the European Union for the treatment of Alzheimer's disease. *Dtsch Apoth Ztg* 1998;**138**(21):43–4. [Non-RCT]

Rivastigmine (Exelon registered) for symptomatic treatment of Alzheimer's disease. *Geneesmiddelenbulletin* 1998;**32**(11):129–30. [Non-English language]

Tacrine. *Prescrire Int* 1999;**8**(39):16–8. [Non-systematic review]

Rivastigmine. *Prescrire Int* 1999;**8**(40):47–8. [Non-systematic review]

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Appendix 14

Drugs under development*

Group and drug	Status	Company
Drugs directed at the cholinergic system		
ACE inhibitors		
Donepezil (Aricept)	Launched 1997	Pfizer, Am Home Prod.
Rivastigmine tartrate (Exelon)	Launched 1998	Novartis
Galantamine	Phase III	Intelligen, Shire, Janssen.
Tacrine	Pre-registration	Warner Lambert USA
Huperzine A	Phase III	Non-industrial
Ipidacrine hydrochloride	Phase III	Nikkel Chemical
Physostigmine	Phase III	Forset
Besipiridine	Phase II/III	HSM
TAK-147	Phase III	Takedo
Icopezile maleate	Phase II	Pfizer
Quilostigmine	Phase II	Astra
Acetylcholine agonist		
Nebracetam	Phase III	Boehringer Ingelheim
Acetylcholine release stimulants		
T-588	Phase II	Toyama
JTP-4819	Phase II	Japan Tabacco
Choline uptake stimulant		
MKC-231	Phase II	Mitsubishi Chemical
Muscarinic M1 agonist		
Stacofylline hydrochlor	Phase II	Servier
Nicotine agonist		
ABT-418		Abbott
Drugs under development, directed at amyloid pathway		
Abetal-196	Preclinical	Elan (Ireland), Lilly (USA)
Amyloid deposit inhibitors	Preclinical	Neurochem (Canada), Warner-Lambert (USA)
Ramot project no. B118	Preclinical	Ramot (Israel)
NC-531	Preclinical	Neurochem (Canada)
Other drugs developed for treatment of AD (excluding acetylcholine-mediated drugs)		
MAO B inhibitor		
Lazabemide	Phase III	Roche
5-Hydroxytryptamine uptake inhibitor		
Indeloxamine	Phase III	Yamanouchi
5-Hydroxytryptamine uptake stimulant		
FK-960	Phase II	Fujisawa
5-Hydroxytryptamine 1A agonist		
SR-57746A	Phase III	Sanofi

continued

* Drugs in different stages of development, with different mechanisms of action for treatment of AD

Group and drug	Status	Company
***Other drugs developed for treatment of AD (excluding acetylcholine-mediated drugs)* contd**		
Alpha 1 adrenoreceptor antagonist		
Nicergoline	Pre-registration	Pharmacia
Phosphodiesterase inhibitor		
Propentofyline	Pre-registration	Hoechst Marion Roussel
N-Methyl-D-aspartate (NMDA) antagonists		
Memantine	Phase III	Merz
Aptiganel (Cerestat)	Phase III	Boehringer Ingelhiem & Cambridge Neuroscience
Serotonin 1A receptor agonist		
SR 57746A	Phase III	Sanofi
AMPA receptor agonist		
AMPAlex	Phase II	Cortex Pharma
Thyrotropin releasing hormone agonist		
Posatirelin	Phase III	Richter, Dainippon
Corticotropin releasing factor agonist		
NBI-30775	Phase II	J&J, Lilly
Membrane permeability enhancer		
Alzene	Phase II	Baker Norton
Excitatory amino acid agonist		
KA-672-HCl	Phase II	Schwabe (Germany)
Immunostimulant		
Colostrinin	Phase II	Rantschler (Germany)
Benzodiazapine inverse agonist		
S-8510	Phase II	Shinogi (Japan)
Nerve growth factor agonist		
Leteprinim potassium	Phase II	Neotherapeutics (USA)
Protein synthesis stimulant		
Dehydroepiandrosterone	Phase III	Neurocrine Biosciences
Unidentified pharmacological activity		
Vitamin D derivative	Phase II	Apollo BioPharmaceutics
HP-9	Phase II	Milkhaus (USA)

Source: National Horizon Scanning Centre Report on Status of Drugs Development Known About in December 1998. Please note that some information about specific drugs or drug companies may have changed

Appendix 15

Research in progress on donepezil, rivastigmine and galantamine

Databases searched

The following electronic databases were searched to identify research in progress or that should be complete but appears to be unpublished: National Research Register, MRC Trials database, Early Warning System and Current Controlled Trials. These were searched for the periods covered by the databases up until July 2000 and were limited to English language studies.

Donepezil

- AD2000 Trial into costs and benefits of ARICEPT for dementia. Gray R; Clinical Trials Unit, University of Birmingham. Start date: 1/1/98. End date: 1/1/2002. Funding: NHS EW Midlands.
- AD2000. Rayner I; Kingstanding CMHT, Birmingham. Start date: 1/6/98. End date: 1/6/2000. Funding: NHS EW Midlands.
- AD2000 A reliable assessment of the efficacy and safety of donepezil and aspirin in Alzheimer's disease. Ehtisham M. City Hospital NHS Trust, Birmingham. Start date: 1/6/98. End date: 31/12/2000. Funding: W Midlands RHA.
- Alzheimer's disease and response to donepezil in the AD2000 trial. Craddock N; Queen Elizabeth Psychiatric Hospital, Birmingham. Start date: 1/5/98. End date: 31/5/2001. Funding: W Midlands RHA.
- A reliable assessment of the efficacy and safety of donepezil and aspirin in Alzheimer's disease (AD2000). Bentham P; South Birmingham Mental Health NHS Trust, Birmingham. Start date: 1/7/97. End date: 31/1/2000. Funding: NHS R&D West Midlands.
- A reliable assessment of the efficacy and safety of donepezil and aspirin in Alzheimer's disease (AD2000). Crome P; School of Postgraduate Medicine, Stoke-on-Trent. Start date: 1/12/98. End date: 1/12/2001. Funding: W Midlands RHA.
- Does Donepezil produce worthwhile improvement in ecologically valid measures of memory and practical ADL performance? Bentham P; South Birmingham Mental Health NHS Trust, Birmingham. Start date: 1/2/98. End date: 29/2/2000. Funding: unknown.
- SDZ ENA 713 in Alzheimer's disease. Rossor M; National Hospital for Neurology and Neurosurgery, London. Start date: 1/1/95. End date: 1/6/99. Funding: Novartis Pharmaceuticals UK Ltd.
- E2020 in Alzheimer's disease. Rossor M; National Hospital for Neurology and Neurosurgery, London. Start date: 1/1/94. End date: 1/12/98. Funding: Eisai UK Ltd.
- The effect of a carer's intervention in patients with Alzheimer's disease on Aricept. Burns A; South Manchester University Hospitals NHS Trust, Manchester. Start date: 1/1/99. End date: 31/12/2001. Funding: unknown.
- A qualitative analysis of the outcomes of Aricept use in community settings. Thompson S; Sussex Weald & Downs NHS Trust, West Sussex. Start date: 30/4/99. End date: 30/4/2001. Funding: Pfizer.

Rivastigmine

- An open-label study to evaluate the safety and tolerability of 1.5 mg bid (3 mg/day) through 6 mg bid (12 mg/day), Exelon in patients with mild to moderate probably Alzheimer's disease in the community setting. Hodges J; Addenbrooke's NHS Trust, Cambridge. Start date: 28/2/97. End date: 28/2/2000. Funding: unknown.

Galantamine

- Long term safety and efficacy of galantamine in the treatment of Alzheimer's disease (GAL-INT-8) (extension protocol to 97/16 approved 29/10/97). Livingston G; Whittington Hospital, London. Start date: 1/6/98. End date: 31/8/2000. Funding: Janssen-Cilag Ltd.
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We look forward to hearing from you.

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