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Abstract

The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease

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Objectives: To provide an update review of the best quality evidence for the clinical effectiveness and cost-effectiveness of donepezil, rivastigmine and galantamine for mild to moderately severe Alzheimer's disease (AD) and of memantine for moderately severe to severe AD.

Data sources: Electronic databases, experts in the field and manufacturer submissions to the National Institute for Health and Clinical Excellence (NICE).

Review methods: A systematic review of the literature and an economic evaluation were undertaken. The quality of included randomised controlled trials (RCTs) was assessed using criteria developed by the NHS Centre for Reviews and Dissemination. An outline assessment of economic evaluations was undertaken using a standard checklist. The clinical and cost-effectiveness data were synthesised through a narrative review with full tabulation of the results of included studies. Where appropriate, meta-analysis of data was undertaken.

Results: For mild to moderately severe AD, the results of the study suggested that all three treatments were beneficial when assessed using cognitive outcome measures. Global outcome measures were positive for donepezil and rivastigmine, but mixed for galantamine. Results for measures of function were mixed for donepezil and rivastigmine, but positive for galantamine. Behaviour and mood measures were mixed for donepezil and galantamine, but showed no benefit for rivastigmine. For memantine, two published RCTs were included; in one of these trials the participants were already being treated with donepezil. The results suggest that memantine is beneficial when assessed using functional and global measurements. The effect of memantine on cognitive and behaviour and mood outcomes is, however, less clear. Literature on the cost-effectiveness of donepezil, rivastigmine and galantamine was dominated by industry-sponsored studies, and studies varied in methods and results. Of the three UK studies, two report donepezil as not cost-effective, whereas a third study reports an additional cost (£1996) of between £1200 and £7000 per year in a non-severe AD health state (concerns over these estimates are raised, suggesting that they may underestimate the true cost-effectiveness of donepezil). Cost-effectiveness analysis undertaken in this review suggests that donepezil treatment has a cost per quality-adjusted life-year (QALY) in excess of £80,000, with donepezil treatment reducing the mean time spent in full-time care (delays progression of AD) by 1.42–1.59 months (over a 5-year period). From four published cost-effectiveness studies, two UK studies report additional costs associated with rivastigmine treatment. Cost-effectiveness analysis undertaken in the current review suggests that rivastigmine treatment has a cost per QALY in excess of £57,000, with rivastigmine treatment reducing the mean time spent in full-time care (delays progression) by 1.43–1.63 months (over a 5-year period). From five published cost-effectiveness studies, one UK study reports a cost per QALY of £8693 for 16-mg galantamine treatment and £10,051 for 24-mg galantamine treatment (concerns raised suggest that this may underestimate the true cost-effectiveness of galantamine). Cost-effectiveness analysis undertaken in the present review suggests that galantamine treatment has a cost per QALY in excess of £68,000, with galantamine reducing the time spent in full-time care (delays progression) by 1.42–1.73 months (over a 5-year period). From two published cost-effectiveness studies, one reports analysis for the UK, finding that memantine treatment results in cost savings and benefits in terms of delaying disease progression (concerns raised suggest that this may underestimate

the true cost-effectiveness of memantine). In the current review, the cost-effectiveness of memantine has not been modelled separately, but where alternative parameter inputs on the cost structure and utility values have been used in a reanalysis using the industry model, the cost-effectiveness is reported at between £37,000 and £52,000 per QALY, with this alternative analysis still based on what is regarded as an optimistic or favourable effectiveness profile for memantine.

Conclusions: Although results from the clinical effectiveness review suggest that these treatments may be beneficial, a number of issues need to be considered when assessing the results of the present review, such as the characteristics of the participants included in the individual trials, the outcome measures used, the length of study duration, the effects of attrition and the relationship between statistical significance and clinical significance. Many included trials were sponsored by industry. For donepezil, rivastigmine and galantamine, the cost savings associated with reducing the mean time spent in full-time care do not offset the cost of treatment sufficiently to bring estimated cost-effectiveness to levels generally considered acceptable by NHS policy makers. It is difficult to draw conclusions on the cost-effectiveness of memantine; it is suggested that further amendments to the potentially optimistic industry model (measure of effect) would offer higher cost per QALY estimates. Future research should include: information on the quality of the outcome measures used; development of quality of life instruments for patients and carers; studies assessing the effects of these interventions of durations longer than 12 months; comparisons of benefits between interventions; and research on the prediction of disease progression.

Contents

List of abbreviations

AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale, cognitive subscale
ADCS/ADL	AD Cooperative Study Activities of Daily Living inventory
ADFACS	Alzheimer's Disease Functional Assessment and Change Scale
ADL	Activities of Daily Living
AE	adverse event
AHEAD	Assessment of Health Economics in Alzheimer's Disease
APP	amyloid precursor protein
BADLS	Bristol Activities of Daily Living Scale
BGP	Behavioural Rating Scale for Geriatric Patients
BNF	British National Formulary
BOI	burden of illness
BVRT	Benton Visual Retention Test
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CCT	controlled clinical trial
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating Scale – Sum of the Boxes
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CGIC	Clinical Global Impression of Change
CGRS	Crichton Geriatric Rating Scale
CI	confidence interval
CIBIC	Clinician's Interview-based Impression of Change
CMB	Computerised Memory Battery
CMCS	Caregiver-rated Modified Crichton Scale
CPS	Cognitive Performance Scale
CSHA	Canadian Study of Health and Aging
CSRI	Client Service Receipt Inventory
CT	computed tomography
CUA	cost–utility analysis
DAD	Disability Assessment for Dementia
DLB	dementia with Lewy bodies
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSS	Department of Social Services
DSST	Digit Symbol Substitution Test
EOAD	early-onset Alzheimer's disease
EPS	extrapyramidal symptoms
FAST	Functioning Assessment Staging Scale
FLD	frontal lobe dementia
FOME	Fuld Object Memory Evaluation
FTC	full-time care
GBS	Gottfries–Bråne–Steen
GDS	Global Deterioration Scale
GHQ-30	General Health Questionnaire 30
HUI	Health Utilities Index (version 2 and 3)
IADL	Instrumental Activities of Daily Living
ICD-10	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
IDDD	Interview for Deterioration in Daily Living Activities in Dementia

continued

List of abbreviations *continued*

IHQL	Index of Health Related Quality of Life
ITT	intention-to-treat
LOCF	last observation carried forward
MENFIS	Mental Function Impairment Scale
MID	multiple-infarct dementia
mMMSE	modified MMSE
MMSE	mini-mental state examination
MDS	Minimum Data Set
MRI	magnetic resonance imaging
NADES	National Dementia Economic Study
NHS CRD	NHS Centre for Reviews and Dissemination
NICE	National Institute for Health and Clinical Excellence
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NMDA	*N*-methyl-D-aspartate
NNT	number-needed-to-treat
NOSGER	Nurses' Observation Scale for Geriatric Patients
NPI	Neuropsychiatric Inventory
NPI-D	Neuropsychiatric Inventory, distress subscale
ns	not significant
NYU	New York University
oc	observed case
OPCS	Office of Population Census and Surveys
OR	odds ratio
PCA	prescription cost analysis
PCT	primary care trust
P&CSQ	Physician's and Caregiver's Satisfaction Questionnaire
PDS	Progressive Deterioration Scale
PGA	Patient Global Assessment Scale
PSMS	Physical Self-Maintenance Scale
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
QoL-C	caregiver-rated quality of life
QoL-P	patient-rated quality of life
QWB	Quality of Well-being Scale
RCT	randomised controlled trial
SD	standard deviation
SDAT	senile dementia of the Alzheimer's type
SEM	standard error of the mean
SEVINT	OPCS measure of intellectual functioning
SHTAC	Southampton Health Technology Assessment Centre
SIB	Severe Impairment Battery
sMMSE	severe MMSE
SMR	standardised mortality ratio
SSD	Social Services Department
TESS	Treatment Emergent Signs and Symptoms
TMT	trail making test
TTO	time trade-off
UPDRS	Unified Parkinson's Disease Rating Scale
VAD	vascular dementia
VAS	visual analogue scale
WIHRD	Wessex Institute for Health Research and Development
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Epidemiology and background

Alzheimer's disease (AD) is the most common cause of dementia and is characterised by an insidious onset and slow deterioration in cognition, functional ability (e.g. activities of daily living) and behaviour and mood. AD prevalence rises with increasing age and the estimated prevalence of AD for a standard primary care trust with a population of 200,000 is approximately 1100. Current service involves a wide range of agencies. In 2001, the National Institute for Health and Clinical Excellence (NICE) recommended that cholinesterase inhibitors (donepezil, rivastigmine, galantamine) should be offered to patients with mild to moderate AD under a number of conditions. Patients with more severe AD may benefit from memantine but there is currently no guidance on its use.

Aim of the review

The aim of this review was to provide an update review of the best quality evidence for the clinical effectiveness and cost-effectiveness of donepezil, rivastigmine, and galantamine for mild to moderately severe AD. It also aimed to provide a review of the best quality evidence for the clinical effectiveness and cost-effectiveness of memantine for moderately severe to severe AD.

Methods

A systematic review of the literature and an economic evaluation were undertaken.

Data sources

Electronic databases were searched from inception to July 2004. Bibliographies of included studies and related papers were checked for relevant studies and experts were contacted for advice and peer review and to identify additional published and unpublished studies. Manufacturer submissions to NICE were reviewed.

Study selection

Studies were included if they met the following criteria.

- Interventions: donepezil, rivastigmine, galantamine or memantine.
- Participants: people diagnosed with Alzheimer's disease who met the criteria for treatment with donepezil, rivastigmine, galantamine or memantine.
- Design: systematic reviews of randomised controlled trials (RCTs) and RCTs comparing the different drugs with placebo or each other or non-drug comparators were included in the review of effectiveness. Economic evaluations including a comparator (or placebo) and both the costs and consequences (outcomes) of treatment were included.
- Primary outcomes: measures of global functioning, cognition, function, behaviour and mood, and health-related quality of life.

Studies in non-English languages were excluded. Studies published only as abstracts or conference presentations were included if sufficient detail was presented. Titles and abstracts were screened for eligibility by one reviewer and checked by a second reviewer. Inclusion criteria were applied to the full text of selected papers by two reviewers. Any differences in opinion were resolved though discussion or consultation with a third reviewer.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with any differences in opinion resolved through discussion. The quality of included RCTs was assessed using criteria developed by the NHS Centre for Reviews and Dissemination. An outline assessment of economic evaluations was undertaken using a standard checklist.

Data synthesis

The clinical and cost-effectiveness data were synthesised through a narrative review with full tabulation of the results of included studies. Where appropriate, meta-analysis of data was undertaken.

Results: clinical effectiveness

Donepezil

Thirteen published RCTs and one unpublished RCT were included. The results suggest that donepezil is beneficial when assessed using global and cognitive outcome measures. There appears to be a dose–response relationship with higher doses more likely to produce benefit. Mixed results were demonstrated on measures of function and behaviour and mood; over shorter durations of follow-up (up to 6 months) donepezil may be beneficial when assessed using these outcome measures.

Rivastigmine

Four published and two unpublished RCTs were included. The results suggest that rivastigmine is beneficial when assessed using global and cognitive outcome measures. The benefits demonstrated may be related to dose, with higher doses more likely to produce benefit. Results for measures of function were mixed: rivastigmine was beneficial at higher doses in some studies. There was no reported beneficial effect of rivastigmine on measures of behaviour and mood.

Galantamine

Six published RCTs and one unpublished RCT were included. The results suggest that galantamine is beneficial when assessed using cognitive and functional outcome measures. The benefits demonstrated may be related to dose, with higher doses more likely to produce benefit. Mixed results were demonstrated on global outcome measures and on measures of behaviour and mood.

Memantine

Two published RCTs were included; in one of these trials the participants were already being treated with donepezil. The results suggest that memantine is beneficial when assessed using functional and global measurements. The effect of memantine on cognitive and behaviour and mood outcomes is, however, less clear.

Results: cost-effectiveness

Donepezil

Nine published economic evaluations of donepezil and the industry submission were included, together with two published abstracts. The literature is dominated by industry-sponsored cost-effectiveness studies and the studies identified report varied methodology and results. There are concerns over the dominant use of mini-mental state examination (MMSE) to consider disease progression, costs and outcomes in the published cost-effectiveness studies, as it has limitations for defining disease severity and also in the modelling of disease progression in AD. From a UK perspective, of three UK studies, two report donepezil as not cost-effective, whereas a third study reports an additional cost (£1996) of between £1200 and £7000 per year in a non-severe AD health state (concerns over these estimates are raised, suggesting that they may underestimate the true cost-effectiveness of donepezil). Cost-effectiveness analysis undertaken in the present review suggests that donepezil treatment has a cost per quality-adjusted life-year (QALY) in excess of £80,000, with donepezil treatment reducing the mean time spent in full-time care (delays progression of AD) by 1.42–1.59 months (over a 5-year period); cost savings associated with this reduction do not offset the cost of treatment sufficiently to bring estimated cost-effectiveness to levels generally considered acceptable by NHS policy makers.

Rivastigmine

Four published economic evaluations of rivastigmine and the industry submission were included, plus one published abstract. The literature is dominated by industry-sponsored cost-effectiveness studies. Cost-effectiveness studies for rivastigmine are based almost solely on methods involving MMSE as a measure of cognitive function, with rivastigmine treatment related to delays in cognitive function and patient benefits over time. As noted above, there are concerns over the use of cognitive function (e.g. MMSE) alone to consider progression of AD. From a UK perspective, two UK cost-effectiveness studies report additional costs associated with rivastigmine treatment. Cost-effectiveness analysis undertaken in the current review suggests that rivastigmine treatment has a cost per QALY in excess of £57,000, with rivastigmine treatment reducing the mean time spent in full-time care (delays progression) by 1.43–1.63 months (over a 5-year period); cost savings associated with this reduction do not offset the cost of treatment sufficiently to make it appear a cost-effective intervention.

Galantamine

Five published economic evaluations of galantamine (industry sponsored) plus the industry submission were included. Cost-effectiveness studies for galantamine have all used the same methodology to model disease progression over time, with country-specific cost-effectiveness studies published. From a UK perspective, one UK study reports a cost per QALY of £8693 for 16-mg galantamine treatment and £10,051 for 24-mg galantamine treatment (concerns over these estimates are raised, suggesting that they may underestimate the true cost-effectiveness of galantamine). Cost-effectiveness analysis undertaken in the present review suggests that galantamine treatment has a cost per QALY in excess of £68,000, with galantamine reducing the time spent in full-time care (delays progression) by 1.42–1.73 months (over a 5-year period); cost savings associated with this reduction do not offset the cost of treatment sufficiently to bring estimated cost-effectiveness to levels generally considered acceptable by NHS policy makers.

Memantine

Two published (in press at the time of the study) economic evaluations and the industry submission were included, plus three published abstracts. Published studies (industry sponsored) have used a similar methodology to consider disease progression for AD. One cost-effectiveness study reports analysis for the UK, finding that memantine treatment results in cost savings and benefits in terms of delaying disease progression (concerns over these estimates are raised, suggesting that they may underestimate the true cost-effectiveness of memantine). In the current review, the cost-effectiveness of memantine has not been modelled separately, but where alternative parameter inputs on the cost structure and utility values have been used in a reanalysis using the industry model, the cost-effectiveness is reported at between £37,000 and £52,000 per QALY, with this alternative analysis still based on what is regarded as an optimistic or favourable effectiveness profile for memantine.

Generalisability of the findings

A number of issues need to be considered when assessing the results of the present review. These include the characteristics of the participants included in the individual trials, the outcome measures used, the length of study duration, the effects of attrition and the relationship between statistical significance and clinical significance. Many included trials were sponsored by industry.

Need for further research

Future research should include: information on the quality of the outcome measures used; development of quality of life instruments for patients and carers; studies assessing the effects of these interventions of durations longer than 12 months; comparisons of benefits between interventions; and research on the prediction of disease progression.

Chapter 1

Aim of the review

This is an update report for donepezil, rivastigmine and galantamine (the first being completed in 2000)[1] and a new report for memantine.

The aim of the review is (1) to provide a review of the clinical effectiveness and cost-effectiveness of the symptomatic treatments of donepezil, rivastigmine and galantamine for people suffering from mild to moderately severe Alzheimer's disease (AD); and (2) to provide a review of the clinical effectiveness and cost-effectiveness of memantine for the symptomatic treatment of people suffering from moderately severe to severe AD. Potential benefits may be demonstrated on measures of global functioning, cognition, function, behaviour and mood and health-related quality of life (QoL). These drugs may also improve the ability to remain independent, reduce the likelihood of admission to residential/nursing care and improve carer health-related QoL.

Chapter 2
Background

Description of underlying health problem

Dementia is a generic term describing chronic or progressive dysfunction of cortical and subcortical function that results in complex cognitive decline. These cognitive changes are commonly accompanied by disturbances of mood, behaviour and personality.[2] AD is the most common cause of dementia. Other causes of dementia include vascular dementia (VAD), dementia with Lewy bodies (DLB) and frontotemporal or frontal lobe dementia (FLD).[3–5]

Dementia in AD is a primary degenerative cerebral disease of unknown aetiology with characteristic neuropathological and neurochemical features. The disorder is usually insidious in onset and it is difficult to set a clear threshold on the continuum between normality and dementia, but this is often defined when cognitive impairment is sufficient to interfere with normal social functioning. AD develops slowly but steadily over a period of several years.

Progression of AD is characterised by a worsening of cognition (thinking, conceiving, reasoning and memory), functional ability (e.g. activities of daily living) and behaviour and mood. Changes in one or more of these domains and their effects on the patient and their carers' well-being provide the basis for diagnosis, assessing severity and progression of the syndrome.

Early onset AD

AD is primarily a disease affecting the elderly. Although largely the same disease, early-onset AD (EOAD) is AD with an onset before age 65 years. It is a rare cause of the disease and these people often have a family history of the disease. Mutations in three genes have been identified in those with a strong family history of the disease [amyloid precursor protein (APP), presenilin-1 and presenilin-2].

Mixed dementia

Despite a differentiation between VAD and AD, current evidence suggests there is some degree of overlap between the two disorders; a proportion of patients with dementia display both vascular and AD-type lesions.[6] This is often described as mixed dementia or atypical dementia.

Risk factors

AD is thought to be caused by many interacting factors. So far only age, family history and the E4 allele of the APOE gene have been confirmed as risk factors for the disease. Other potential risk factors are hypertension, vascular pathology, head injury and herpes simplex infection.[2]

Diagnosis

AD is the most common cause of dementia and its characteristic insidious onset with slow deterioration makes diagnosis difficult. In the majority of cases the diagnosis is one of exclusion; AD is diagnosed once other causes of dementia have been excluded. AD is diagnosed on the basis of a review of a full medical history corroborated by a close relative or carer, physical examination, blood investigations and mental state examination, including cognitive assessment. 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. This is usually made only on post-mortem examination. Several different diagnostic criteria for AD have been developed. The most generally accepted clinical diagnostic criteria are those of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[7] (McKhann criteria), the Diagnostic and Statistical Manual of Mental Disorders (DSM), currently version IV (DSM-IV), and the International Classification of Diseases (ICD-10) (see Appendix 1).

The NINCDS-ADRDA provides clinical guidance for 'possible', 'probable' and 'definite' diagnosis of AD. A diagnosis of possible AD is made when no other disease appears to be primarily responsible for the dementia or when the onset of symptoms is not typical of AD. A diagnosis of probable AD requires a patient to have dementia and a history and pattern of symptoms consistent with those generally seen in AD. Definite AD is diagnosed when evidence is shown through brain biopsy or at autopsy. The sensitivity and specificity of the

criteria have been estimated as 0.81–0.92 and 0.13–0.80, respectively, compared with pathological diagnosis.[8] These criteria are widely used in research in the UK, including in clinical trials.

Diagnosis is also often made according to the DSM criteria. The DSM criteria include: loss of intellectual ability, with resulting social and occupational handicap; memory impairment at all levels of encoding, storage and retrieval; one or more of impaired thinking and judgement; and aphasia, apraxia, agnosia, constructional difficulties and personality changes (see Appendix 1 for full details). The DSM-IV is based on clinical judgement. It is reasonably broad and lacks detailed clinical and radiological guidelines.

The ICD-10 requires the presence of a dementia with characteristic neuropathological and neurochemical features, insidious onset with slow deterioration and an absence of clinical evidence to suggest that the mental state may be due to other systemic or brain disease which can induce a dementia (see Appendix 1 for further details). It defines two subtypes: early onset (dementia in AD beginning before the age of 65 years with relatively rapid deterioration and marked multiple disorders of the higher cortical functions); and late onset (clinically observable onset after the age of 65 years and usually in the late 70s or thereafter, with a slow progression, and usually with memory impairment as the principal feature).

Severity

There are a number of different methods of assessing the severity of AD, including: Clinician's Interview-based Impression of Change (CIBIC) and Clinical Dementia Rating (CDR) for global outcome; Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) and mini-mental state examination (MMSE) for severity of cognitive impairment; and Progressive Deterioration Scale (PDS) for functional/QoL outcome. For severity of cognitive impairment, the 30-point MMSE is commonly used in clinical trials. Although there is no range of scores that can be rigidly and universally applied to indicate dementia severity, mild AD is often associated with an MMSE of 21–26, moderate AD with an MMSE of 10–20 and severe AD with an MMSE of <10 (see Appendix 6 for full details of these severity rating scales).

Prevalence and incidence

Prevalence

AD is the most common dementia (around 61% of dementias).[3] A recent pooled estimate from European population-based studies of persons aged ≥65 years identified an age-standardised prevalence of 4.4%.[9] The prevalence among the population with dementia varies from between 37 and 78%.[3,5,9,10] These ranges reflect diagnostic difficulties, the use of different diagnostic criteria and the high frequency of mixed pathology.[4,11,12] Over 30% of patients with AD have been found to have vascular pathology on post mortem.[13,14]

Age-related prevalence

Dementia is a disease of older people. In a review of the prevalence of any-cause dementia, Fratiglioni and colleagues found that dementia occurred in only 1% of 60-year-olds but was present in over 30% of 90-year-olds.[3] A number of population-based studies have estimated the age-specific prevalence of AD. Lobo and colleagues[9] pooled prevalence rates from 11 European studies and demonstrated that prevalence increased continuously with age: for the groups aged 65–69, 70–74, 75–79, 80–84, 85–89 and ≥90 years the prevalence was 0.6, 1.5, 1.8, 6.3, 8.8 and 17.6% in men and 0.7, 2.3, 4.3, 8.4, 14.2 and 23.6% in women. Prevalence of early onset AD has been studied to a lesser extent. In an earlier collaborative study (1980–90), Rocca[10] found that overall European prevalence in those aged 30–59 years was 0.02%.

Gender-related prevalence

AD occurs slightly more commonly in women, particularly those over 75 years of age.[15] In each individual study pooled by Lobo and colleagues,[9] the prevalence was higher in women than in men. The pooled estimates are discussed above.

Severity of dementia

There are few studies on prevalence by severity. Two community-based surveys report MMSE, which has been used to define severity in some clinical trials.[16,17] Some 50–64% of those with AD had scores between 13 and 24 (mild/moderate severity). Although this range is narrower than those used in some clinical trials, it provides an estimate of the likely proportion that might be considered for treatment on the basis of severity alone. Similarly, Pitt and colleagues[18] suggest that about 60% of patients with AD will be classed as minimal, mild or moderate in disease severity. Evans and colleagues,[19] using non-specified cognitive measures, classified 74% of people diagnosed with AD in a community (non-institutionalised) sample as mild to moderately impaired.

TABLE 1 *Estimated prevalence of AD by age in England and Wales*

Age group (years)	Population of England and Wales					
	Males	Females	Prevalence of AD (rate/100 people)		Estimated prevalence of AD	
			Male	Female	Males	Females
65–69	1,116,000	1,199,000	0.6	0.7	6,696	8,393
70–74	950,000	1,126,000	1.5	2.3	14,250	25,898
75–79	731,000	999,000	1.8	4.3	13,158	42,957
80–84	470,000	786,000	6.3	8.4	29,610	66,024
85–89	204,000	458,000	8.8	14.2	17,952	65,036
Total 65+					81,666	208,308

Based on population data from mid-2002 estimates.

TABLE 2 *Estimated prevalence of AD by age for a standard PCT*

Age group (years)	Standard PCT (200,000 people)				
	Population	Prevalence of AD (rate/100 people)		Estimated prevalence of AD	Estimated prevalence of mild to moderate AD
		Male	Female		
65–69	8822	0.6	0.7	58	29–37
70–74	7911	1.5	2.3	153	76–98
75–79	6593	1.8	4.3	213	106–136
80–84	4786	6.3	8.4	364	182–233
85–89	1823	8.8	14.2	316	158–202
Total 65+				1104	551–706

Estimated prevalence for England and Wales

Table 1 uses the prevalence rates for AD from the pooled estimates in the study by Lobo and colleagues[9] to provide an estimate of the prevalence of AD for the population of England and Wales (based on mid-2002 population estimates).[20] This shows that there are approximately 290,000 people in England and Wales with AD. Assuming that 50–64% of people with AD have the mild to moderate form of the disease we would expect to find between 145,000 and 185,600 cases of mild to moderate disease.

Estimated prevalence for primary care trust

Table 2 uses the same prevalence rates for AD as above to provide an estimate of the prevalence of AD for an average population of a primary care trust (PCT). A PCT with a population of 200,000 might expect to have approximately 30,000 people over the age of 65 years and approximately 1100 cases of AD. It can also be seen in *Table 2* that, assuming that 50–64% of people with AD have the mild to moderate form of the disease, a PCT might expect to have between 551 and 706 cases of mild to moderate disease.

Incidence

The 1-year incidence of all-cause dementia increases from 0.01 per 1000 population at 65 years to 80 per 1000 at age 85 years.[3] The incidence of AD appears to have been stable over the past two decades, although demographic changes (e.g. ageing population) may result in an increase in prevalence in the future.[16] Incidence rates for AD in those aged over 65 years from recent studies range from 4.9 per 1000 person-years[21] in a UK study; 6.55 [95% confidence interval (CI) 4.92 to 8.17] per 1000 person-years in an Italian study;[22] and 14.26 (95% CI: 12.2 to 16.7)[23] in a US study.

Age-related incidence

A recent pooled estimate from eight European population-based studies of persons aged ≥65 years demonstrated rising incidence rates with increasing age.[24] The age-specific incidence

rates for those aged 65–69, 70–74, 75–79, 80–84, 85–89 and ≥ 90 years was 1.2, 3.3, 9.1, 21.8, 35.3 and 53.5 per 1000 person years, respectively. Incidence rates across the pooled studies varied owing to small numbers in some, particularly in the more elderly male groups.

Gender-related incidence

Previous studies suggest that women have a higher risk of dementia than men. Pooled analysis from eight population-based studies[24] showed that incidence rates among women were higher than those in men. In addition, rates among women increased more steeply by age than they did in men. Incidence rates increased continuously with age: for the groups aged 65–69, 70–74, 75–79, 80–84, 85–89 and ≥ 90 years the incidence rates were 0.9. 3.0, 6.9, 14.8, 24.2 and 20.0 per 1000 person-years in men and 2.2, 3.8, 10.3, 27.3, 41.5 and 69.7 per 1000 person-years in women. An earlier pooled analysis from four population-based prospective cohort studies[25] showed that there were significant gender differences in the incidence of AD after age 85 years. At 90 years the rate was 81.7 per 1000 person-years (95% CI: 63.8 to 104.7) in women and 24.0 per 1000 person-years (95% CI: 10.3 to 55.6) in men.

Current service provision

Help-seeking, diagnosis and care of people with dementia depend on the course and particular symptoms of dementia in an individual, the subtype of dementia and other patient characteristics such as co-morbid physical disorder and personality. Patients may complain of forgetfulness, decline in mental functioning or feeling depressed, but may be unaware or deny the extent of memory loss and other deterioration in functioning. Dementia may be diagnosed first during consultations for other problems, or may result from families asking for help because of failing memory, disorientation, self-care, change in personality or behaviour. In the later stages of the illness, relatives of people with dementia may seek help because of behavioural disturbance, wandering or incontinence or an episode of dangerous behaviour. Many patients and relatives may believe deterioration in memory and function to be a natural part of ageing and consequently may not present to their GP, until behaviour and functional problems occur after 2–3 years from the first symptoms of memory loss.

Formal recognition of dementia in primary care can therefore be low, particularly in the early stages. Those recognised are generally referred to old-age psychiatric services. However, depending on the local availability of memory clinics, some people with early symptoms may be referred directly to a memory clinic for diagnosis and management. Holmes and colleagues[26] estimated that only 10–15% of people with dementia receive something in the way of a specialist assessment of treatment at any stage in their illness. It is thought that this may have increased with introduction of cholinesterase inhibitors (see below).

Good-quality dementia care will often require a package of care, with coordinated contributions from a number of services. Most care is provided by family carers (the term 'family carer' has been used to include any non-professional carers as this is preferred by user groups) but accurate and effective professional help is also often needed. With respect to the medical elements of diagnosis and care, there is at present no consensus on what can and should be done in primary care and what requires referral to secondary care. In practice, there is substantial variation in how services are provided for people with dementia, with a lack of coherent diagnosis and care planning the norm.[27]

Management of dementia often involves attending to the needs of family carers in addition to the treatment of cognitive symptoms, non-cognitive symptoms such as agitation and hallucinations and any other coexisting illnesses such as depression. Non-pharmacological therapies such as memory training and orientation therapy are not routine as a means of improving cognition as there is little evidence for their effectiveness for this end-point.[28,29] Non-pharmacological treatments are valuable, however, in allowing the patient and their families to manage symptoms, and therapies such as reminiscence therapy may be used, for example, to re-establish rapport between carers and patients. Limitations in resources and personnel (particularly clinical psychologists and occupational therapists), however, limit the availability of such techniques. Education and support from statutory services and from the voluntary sector are also valuable interventions in the management of dementia. Another important aspect of dementia care and management is the planning of future care before the patient loses the capacity to make choices.

In 2001, the National Institute for Health and Clinical Excellence (NICE)[30] recommended that cholinesterase inhibitors (donepezil, rivastigmine, galantamine) should be offered to patients with mild to moderate AD, whose MMSE is above 12,

as one component of their care. A number of conditions to the use of the drugs were suggested, including:

- Diagnosis that the form of dementia is AD must be made in a specialist clinic according to standard diagnostic criteria.
- Assessment in a specialist clinic, including tests of cognitive, global and behavioural functioning and of activities of daily living, should be made before the drug is prescribed.
- Clinicians should also exercise judgement about the likelihood of compliance; in general, a carer or care-worker who is in sufficient contact with the patient to ensure compliance should be a minimum requirement.
- Only specialists (including old-age psychiatrists, neurologists and care of the elderly physicians) should initiate treatment. Carers' views of the patient's condition at baseline and follow-up should be sought. If GPs are to control prescribing, it is recommended that they should do so under an agreed shared-care protocol with clear treatment endpoints.
- A further assessment should be made, usually 2–4 months after reaching maintenance dose of the drug. Following this assessment, the drug should be continued only where there has been an improvement or no deterioration in MMSE score, together with evidence of global improvement on the basis of behavioural and/or functional assessment.
- Patients who continue on the drug should be reviewed by MMSE score and global, functional and behavioural assessment every 6 months. The drug should normally only be continued while their MMSE score remains above 12 points and their global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect. When the MMSE score falls below 12 points, patients should not normally be prescribed any of these three drugs. Any review involving MMSE assessment should be undertaken by an appropriate specialist team, unless there are locally agreed protocols for shared care.

These recommendations have resulted in a change in the provision of dementia services. Increased demand has generally been met by stretching existing resources within generic old-age psychiatric services, leading to a relatively low penetration into the pool of unmet need for care in dementia. One response has been to establish memory clinics; however, these vary from large centres of research excellence to more traditional outpatient-style clinics. Memory clinics have the capacity to see only a small proportion of people with dementia and are currently not universally available.[31] The role of specialist services and memory clinics has been further clarified by the National Service Framework for Older People.[32] This states that patients should be referred to specialist services for diagnostic uncertainty, for consideration of drug therapy or if the patient is a danger to themselves or others, such as in consideration of fitness to drive.

Current best practice is for care of the person with AD to be provided by a multidisciplinary team. This may consist of a consultant old-age psychiatrist, community mental health nurses, clinical psychologists, occupational therapists and social workers. Additional support may be provided by other professionals allied to medicine and community services such as domiciliary care, outpatients services, outreach services and daycare.[32] The aim of treatment is to support patients in the community and in their own homes if possible. In addition, dementia patients may have access to day hospitals and acute and rehabilitation hospital beds. Other aspects of care consist of financial and legal support and help for carers (Mather R, Oxford Memory Clinic, Personal communication; 2004; Buss L, Southampton Memory Clinic, Personal communication; 2004[33]).

Patients with more severe dementia may benefit from memantine, which is licensed for the treatment of moderate to severe AD, although there is currently no guidance on its use.

Day-to-day care for those with dementia is frequently undertaken by family carers. Caring for someone with dementia can be very burdensome; people with dementia may have communication difficulties, challenging behaviour, incontinence, problems with eating and difficulties with other activities of daily living[34] and carers require extra support. In many cases these family carers are frail themselves. In some cases support can be provided by the local authority, for example by equipment and house adaptations, 'home help', 'meals-on-wheels' and occasionally respite care schemes; however, these are often limited resources for carers and the level of assistance can differ between local authorities.[35] Residential and nursing homes provide an essential contribution towards the care of people with dementia, with most people with dementia cared for within the private sector[36] with social services contributing to the cost of care on a means-tested basis.

Description of the interventions considered in this review

Four drugs are considered in this review. Three of these drugs are acetylcholinesterase inhibitors (AChEIs). These were developed when it was recognised that AD is associated with reduced levels of the neurotransmitter acetylcholine.[37] AChEIs inhibit acetylcholinesterase, an enzyme responsible for the destruction of acetylcholine. This leads to increased concentrations of acetylcholine in the brain, and the increased concentrations are believed to be responsible for the improvement seen during treatment. Further effects such as altering the underlying pathology may also be relevant, although these have not been studied in detail. The AChEIs improve the symptoms but do not slow the progression of AD. The fourth drug (memantine) is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor inhibitor. It blocks the excessive release of glutamate, which is thought to be associated with cholinergic damage.

Donepezil

Donepezil (Aricept, produced by Eisai and co-marketed with Pfizer) was licensed in 1997 and was the first drug to be licensed in the UK specifically for AD. Donepezil is a reversible, highly specific inhibitor of acetylcholinesterase. Absorption of donepezil is complete and uninfluenced by either food or time of administration. Donepezil is administered once a day and is available in 5- and 10-mg preparations, the lower dose often being prescribed initially.

It must be used with caution in cases of sick sinus syndrome or other supraventricular conduction abnormalities, asthma and obstructive airways disease. Side-effects include diarrhoea, cramps, fatigue, nausea and dizziness.

Rivastigmine

Rivastigmine (Exelon, produced by Novartis Pharmaceuticals) was licensed in the UK for AD in 1998. It is a selective inhibitor of acetylcholinesterase and also butyrylcholinesterase, another enzyme. It has a short half-life, necessitating twice daily dosing, initially starting with a low dose of 3 mg per day and increasing to between 6 and 12 mg per day.

It must be used with caution in cases of 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. Side-effects are typically gastrointestinal related, such as nausea and vomiting, and these occur predominantly in the dose escalation phase.

Galantamine

Galantamine (Reminyl, produced by Shire Pharmaceuticals Group) is licensed for mild to moderate AD. It is a tertiary alkaloid originally isolated from bulbs of snowdrop and narcissus but now produced synthetically. It is a reversible inhibitor of acetylcholinesterase. In addition, galantamine enhances the intrinsic action of acetylcholine on nicotinic receptors, probably through binding to an allosteric site of the receptor. Galantamine has a half-life of about 6 hours. The recommended maintenance dose is 16–24 mg daily taken twice daily.

It must be used with caution in cases of renal impairment, sick sinus syndrome, conduction abnormalities, gastric or duodenal ulcers and a history of asthma or obstructive pulmonary disease. Side-effects may include nausea, vomiting (transient), diarrhoea and abdominal pain.

Memantine

Memantine (Ebixa, produced by Lundbeck) was launched in October 2002 for the treatment of moderate–severe AD. Memantine acts on glutamatergic neurotransmission. Glutamate is an excitatory neurotransmitter in the brain. A pathological release of glutamate is associated with acute and chronic neurodegenerative processes. Memantine is an uncompetitive modulator of the NMDA receptor channel and works through normalisation of glutamatergic neurotransmission. Memantine is administered orally twice daily. The starting dose is 5 mg and this can be increased to a maximum daily dose of 20 mg.

It must be used with caution in renal failure and is not recommended in patients with severe renal impairment. It should also be used with caution in patients with epilepsy. Side-effects may include dizziness, confusion and headache.

Chapter 3
Methods

The *a priori* methods used for systematically reviewing evidence of clinical effectiveness were described in the research protocol (Appendix 2), which was sent for expert comments to peer reviewers. 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, as follows:

- The review should search for controlled clinical trials (CCTs) if no randomised controlled trial (RCT) evidence over 12 months' duration was identified.
- The addition of compliance as an outcome.

The methods outlined in the protocol (Appendix 2) are briefly summarised below.

Inclusion criteria

Interventions included the four drugs donepezil, rivastigmine, galantamine and memantine for AD.

Participants included those people diagnosed with probable AD (NINCDS-ADRDA and/or DSM-III/IV criteria) that met the criteria for treatment with donepezil, rivastigmine, galantamine (mild to moderately severe AD, usually associated with an MMSE score of 10–26) and memantine (moderately severe to severe AD). See Appendix 2 for a fuller description of the participants included.

Systematic reviews of RCTs and RCTs comparing the different drugs with placebo or each other or non-drug comparators were included in the review of effectiveness. Systematic reviews were used as a source for RCTs and as a comparator. Any studies published as abstracts or conference presentations were assessed for inclusion if sufficient details were presented to make appropriate decisions about the methodology of the study and the results. CCTs meeting the other inclusion criteria were also included if they had a duration of follow-up longer than 12 months.

Outcomes focused on those that are clinically relevant to people with AD and their carers. Primary outcome measures included measures of global functioning, cognition, function, behaviour and mood and health-related QoL. In addition, the systematic review reported information on secondary outcomes on adverse events, ability to remain independent, likelihood of admission to residential/nursing care, carer health-related QoL and compliance (adherence).

Inclusion criteria and data extraction process

Studies identified by the search strategy were assessed for inclusion through two stages. The titles and abstracts of all identified studies were screened by two independent reviewers and full-text versions of relevant papers were retrieved. Inclusion criteria of full-text papers were applied by two independent reviewers; any differences in judgement were resolved through discussion. Data were extracted by one reviewer using a standard data extraction form and checked by a second reviewer. At each stage, any differences in opinion were resolved through discussion.

Sources of information, search terms and a flowchart outlining the identification of studies are described in Appendix 3.

Studies excluded from the review, including those reported only as abstracts, are listed in Appendix 4. Full data extraction forms of all the included trials can be seen in Appendices 7–11.

Quality assessment

The quality of included trials was assessed using modified criteria recommended by the NHS Centre for Reviews and Dissemination (CRD; University of York) (see Appendix 5 for full details, and below for the more specific interpretation used in the current review).[38] Economic evaluations were assessed using a modified version of the criteria recommended by Drummond and Jefferson.[39] Quality criteria were

applied by one reviewer and checked by a second reviewer. Any disagreements were resolved through discussion. The assessment of the quality of included trials was limited to published data only (see discussion, strengths and limitations of the review).

A number of 'rules' for describing the quality of included trials were prespecified in the current review to supplement those in Appendix 5; these are the interpretation of the current review only and include the following:

Adequate descriptions:
- Randomisation: randomisation by computerised randomisation schedule whether or not on-site, use of random tables.
- Allocation concealment: states that randomisation schedule was concealed from all personnel, and/or describes how this was undertaken, and/or randomisation was by computerised schedule off-site.
- Blinding of care provider (clinician) and patient: states medications identical in appearance/matched.
- Blinding of assessor: when stated that testing undertaken by an assessor blinded to treatment status or that investigators remained blind to the treatment group.
- Eligibility: if prestated.
- Reporting outcomes: if mean ± standard error of the mean (SEM)/standard deviation (SD)/confidence interval (CI) and others given for all outcomes.
- Intention-to-treat (ITT): if all patients who were randomised regardless as to whether they had any outcome assessment are included in the analysis.
- Withdrawals: if states numbers and provides reasons for withdrawal.

Unknown descriptions:
- Randomisation: when the term randomisation is the only description.
- Allocation concealment: when no description is given. Unable to assume that using a computerised randomisation schedule equals adequate allocation concealment unless stated that undertaken off-site as it could have been a printed list.
- Blinding of care provider and patient: when no descriptions are given.
- Blinding of assessor: when no descriptions are given.
- Eligibility: if not prestated.
- Baseline: no baseline characteristics given and/or states that baselines were similar without giving data, and/or baselines given only for a subset.
- Reporting outcomes: not a response used.
- ITT: not a response used.
- Withdrawals: no details given anywhere of numbers withdrawing, including the *N*s in the tables.

Inadequate descriptions:
- Randomisation: states randomised but method clearly is not (chronological order, case numbers, etc.)
- Allocation concealment: relates to method of randomisation above (so if method is consecutive patients, etc., then inadequate); also, if states allocation not concealed or the method used suggests that concealment is not likely.
- Blinding of care provider and patient: states open study, or that placebo completely different.
- Blinding of assessor: when paper states that assessor was not blinded.
- Eligibility: if not prestated.
- Reporting outcomes: when no measures of variance are provided for any of the outcomes reported.
- ITT: when does not mention ITT/when states used ITT but method is incorrect, such as last observation carried forward (LOCF) where some patients withdrew before any 'observations' were made.
- Withdrawals: where numbers clearly do not add up, or where numbers are only given for the total group not numbers for each arm.

Partial descriptions:
- Randomisation: where states envelopes were used but no further details reported.
- Allocation concealment: not a response used.
- Blinding of care provider and patient: just uses the term double-blind but no further description.
- Blinding of assessor: when blinding of outcome assessor to one outcome, such as adverse events, but does not make it entirely clear whether blinded to treatment group for all outcomes.
- Eligibility: if only minimal data presented or just the total group data are presented.
- Reporting outcomes: when measures of variance are provided for some outcomes but not all outcomes.
- ITT: not a response used.
- Withdrawals: where numbers are given but no reasons or numbers and reasons given but where some still appear to be unaccounted for.

Reported descriptions:
- Only available for baseline characteristics.

Data synthesis

Data were synthesised through a narrative review with tabulation of all eligible studies. Data on a number of outcomes were combined in a meta-analysis summarising the weighted mean difference (WMD) using the fixed-effect and random-effects models using Cochrane Review Manager Software 4.2. Where there was no difference between these two approaches, only the fixed-effect models are presented.

In many cases, individual trials were omitted from the meta-analysis for one or more of a number of reasons. In many publications the data presented were in a graphical form only. Although data were estimated it was often not possible to extract the measures of variance around the point estimates. Where possible the appropriate measure of variance was calculated using published equations presented in the Cochrane Reviewers Handbook.[40] Where data were only presented as a *p*-value for statistical significance, it was not possible to calculate the appropriate measure of variance because the *p*-values had either been generated from non-parametric tests or the statistical tests used were not *t*-tests. Many trials report different dosages of the treatment drug and only where similar doses were reported was it possible to combine data. Some trials had populations that the reviewers felt were too dissimilar for pooling, for example, moderately severe patients only, or those who had already undergone treatment with the treatment drug prior to randomisation. In all cases, only data reported to be from the ITT population were pooled. Despite being unable to meta-analyse all included trials, the narrative review reports all data from all of the included trials, as recommended in the Cochrane Reviewers Handbook.[40]

The meta-analysis was based on the best available data from the included trials. Where ITT data were not available the LOCF data were used. Caution may be required in the interpretation of these data as carrying over early endpoint data may underestimate the decline expected in a condition such as AD. In particular, this may be likely where withdrawals between intervention groups and control groups are non-random. The current review has provided numbers of withdrawals between groups from each study where data were available, which may aid the reader when interpreting the results shown.

Methods for the systematic review of economic evaluations

A systematic literature search was undertaken to identify economic evaluations comparing donepezil, rivastigmine, galantamine and memantine plus best supportive care with best supportive care alone (or with one another). The details of databases searched and search strategy are documented in Appendix 3. Manufacturers' and sponsors' submissions to NICE were reviewed for additional studies.

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by two reviewers, with any disagreement resolved through discussion and referral to a third reviewer if necessary. The full text of relevant papers was obtained and inclusion criteria were applied.

Economic evaluations were eligible for inclusion if they reported on the cost-effectiveness of included pharmaceuticals with AD in the licensed indication.

In some instances, studies that did not meet the inclusion criteria for the review of clinical effectiveness were included in the review of cost-effectiveness.

Chapter 4
Clinical effectiveness

Donepezil

Quantity and quality of research

Thirteen published RCTs and one unpublished RCT met the inclusion criteria for the review. Details of the study characteristics are given in *Table 3*. Twelve published studies report data on participants with mild to moderately severe AD, although the classification of mild to moderately severe AD differs within individual trials, the details of which can be seen in *Table 3*. One RCT reports data on those with moderately severe AD.[41] In this trial the participants are a subgroup from an RCT that did not meet the inclusion criteria for the present review as some participants had severe AD.[42] This study was included as it was accepted to have sufficient power to detect any differences within the subgroups, although this would be less than in the main analyses. One included trial[43] allowed the inclusion of patients with vascular dementia; however, the predominant disorder was AD and therefore the trial met the present review inclusion criteria (see Appendix 2). Eight published RCTs were parallel comparisons of donepezil with placebo,[41,43–49] three RCTs compared two doses of donepezil with placebo,[50–52] one compared three doses of donepezil with placebo[53] and one was a crossover comparison of donepezil with placebo.[54]

One unpublished RCT reports data on participants with mild AD.[55]

In four of the eight trials with a two-arm comparison, the dose of donepezil was 5 mg/day for 28 days followed by 10 mg/day for the remainder of the study duration,[41,45-47] and in another the dose of donepezil was 5 mg/day for 42 days followed by 10 mg/day for the remainder of the study duration.[55] In one the dose was 5 mg/day,[44] in another the dose was 5 or 10 mg donepezil per day[43] and in one the dose was 10 mg/day.[48] **[Commercial/academic confidential information removed]** In all three studies with a three-arm comparison the doses of donepezil were 5 and 10 mg/day in the two treatment groups, respectively. The treatment groups in the four-arm trial had doses of donepezil of 1, 3 and 5 mg/day.[53] The study dose of donepezil in the crossover study was 5 mg. All trials were multicentre studies with sample size ranging from 60 to 473. Nine published RCTs[41,43,46,47,49,50,52–54] calculated the sample size required and all but two of these were able to recruit adequate samples.[43,47] **[Commercial/academic confidential information removed]** The duration of treatment was 12 weeks in three studies,[48,52,53] 24 weeks in seven,[41,44,45,49–51,54] 52 weeks in one,[47] 54 weeks in one[46] and 60 weeks in another.[43] The duration of treatment in the unpublished trial was 24 weeks.[55]

Two included trials had a prerandomisation open-label wash-in with all patients receiving donepezil.[48,49] One included trial used prerandomisation, where there was a randomised run-in period of 12 weeks.[43] This study also had a 6-week no-treatment washout after 60 weeks, and thereafter some participants continued to be evaluated. Owing to the numbers of dropouts the data from the additional evaluations are not discussed in the present review except in the cases where no interim (60-week) data are provided.

The quality of reporting and methodology of the included published RCTs was generally mixed (see *Table 4*). The method of randomisation was adequate in only six studies; however, adequate concealment of allocation was reported in only two of these.[49,54] Therefore, most of the studies included in this review may be subject to selection bias, with the allocation sequence open to possible manipulation. All but one of the RCTs reported adequate eligibility criteria; the one only partially reporting eligibility criteria was the subgroup study.[41] All studies report whether their comparison groups were similar at baseline or not.

Thirteen trials were described as double-blind. Four of these describe the placebo as identical and were judged to be adequately blinded for both the care provider and patient.[43,45,49,54] The remainder described the trial as double-blind without further description of procedures and as such are classified as partial. Blinding of outcome assessors was judged to be adequate in only three studies.[46,52,54] In three studies the reporting suggests that the outcome assessors were blinded for some of the outcomes reported,[43,50,51] whereas the remaining seven studies do not mention blinding of outcome assessors. This factor is

TABLE 3 *Characteristics of included studies for donepezil*

Study	Methods	Participants	Outcomes
AD2000, 2004[43]	*Design*: RCT, double-blind multicentre *Interventions*: 1. 5 or 10 mg/day donepezil 2. Placebo *Number of centres*: 22 *Duration of treatment*: until judged appropriate to stop, 60 weeks mainly reported here as large dropout rate after this time *Sponsor*: NHS research funding	*Inclusion criteria*: AD diagnosed by DSM-IV where there was uncertainty about the benefits of medication; MMSE 10–26 (1 had MMSE 27 in donepezil group); all were in a 12-week randomised run-in period prior to randomisation *Numbers*: 486 randomised 1. 242 to donepezil 2. 244 to placebo *Median age (range)*: 1. 76 (54–93) 2. 75 (46–90)	*Primary outcomes*: • Entry to institutional care • Progression of disability *Secondary outcomes*: • BADLS • MMSE • NPI • Carers' GHQ • Adverse events
Burns *et al.*, 1999[50]	*Design*: RCT, double-blind multicentre *Interventions*: 1. 5 mg/day donepezil 2. 10 mg/day donepezil (5 mg/day for the first 7 days, then 10 mg/day for remainder) 3. Placebo *Number of centres*: 82 *Duration of treatment*: 24 weeks *Sponsor*: Eisai (USA) and Eisai (Japan)	*Inclusion criteria*: aged ≥ 50 years; probable AD (DSM-III-R and NINCDS-ADRDA); MMSE 10–26; CDR 1 or 2 *Numbers*: 1. 271 to 5 mg/day 2. 273 to 10 mg/day 3. 274 to placebo *Mean age ± SE (range)*: 1. 72 ± 0.5 (51–91) 2. 72 ± 0.5 (53–93) 3. 71 ± 0.5 (50–90)	*Primary outcomes*: • ADAS-cog • CIBIC-plus *Secondary outcomes*: • CDR-SB • IDDD • Patient-rated QoL • Adverse events
Gauthier *et al.*, 2002[41]	Design: substudy of moderate patients in Feldman[42] multicentre, double-blind RCT *Interventions*: 1. donepezil 5 mg/day for 28 days (single dosage) followed by an increase to 10 mg/day 2. placebo *Number of centres*: 3 *Duration of treatment*: 24 weeks *Sponsor*: Pfizer and Eisai	*Inclusion criteria*: subanalysis patients met criteria for AD and had MMSE scores of 10–17 *Numbers*: 1. 102 to donepezil 2. 105 to placebo *Mean age (range)*: 1. 74.3 (52–92) 2. 74.3 (48–90)	*Primary outcomes*: • CIBIC-plus *Secondary outcomes*: • sMMSE • Severe Impairment Battery (SIB) • DAD • IADL+ • Physical Self-maintenance Scale (PSMS+) • NPI • Adverse events
Greenberg *et al.*, 2000[54]	*Design*: two-centre, randomised, placebo-controlled, double-blind, crossover study *Interventions*: 1. placebo followed by donepezil 5 mg/day 2. donepezil 5 mg/day followed by placebo *Number of centres*: 2 *Duration of treatment*: 24 weeks, 6 weeks of run-in followed by 18 weeks of treatment, washout and a second treatment period. *Sponsor*: National Institute of Aging (through Massachusetts Alzheimer's Disease Research Center); Massachusetts General Hospital; Mallinckrodt General Clinical Research Center	*Inclusion criteria*: diagnosis of probable AD. Ability to undergo cognitive testing (defined as an information–memory–concentration subscale score of ≤ 20) indicating mild to moderate dementia. *Numbers*: 60 randomised to a crossover sequence, 30 in group 1 and 30 in group 2 *Mean age ± SD*: 1. 74.9 ± 10.1 2. 75.1 ± 9.0 Total 75.0 ± 9.5	*Primary outcomes*: • ADAS-cog *Secondary outcomes*: • Explicit verbal recall (assessed by NYU Stories Test, delayed recognition subscale) • Verbal fluency • Caregiver-rated global impression of change • Compliance • Adverse events

continued

TABLE 3 *Characteristics of included studies for donepezil (cont'd)*

Study	Methods	Participants	Outcomes
Holmes *et al.*, 2004[49]	*Design*: RCT, multicentre *Interventions*: 1. donepezil 10 mg/day 2. placebo *Number of centres*: 16 *Duration of treatment*: 24 weeks (12 weeks open-label donepezil), 6 weeks randomised treatment. Provided there was no marked deterioration (a loss of ≥ 2 points on MMSE) after 6 weeks, continued to 24 weeks *Sponsor*: Pfizer and Eisai	*Inclusion criteria*: aged ≥ 55 years; probable mild to moderate AD (NINCDS-ADRDA); MMSE 10–27; NPI > 11 points. Patients entered an open-label donepezil phase for 12 weeks and were then randomised *Numbers*: 96 participants randomised 1. 41 to donepezil 10 mg/day 2. 55 to placebo *Mean age ± SEM*: 1. 78.6 (1.4) 2. 78.8 (1.2)	*Primary outcomes*: • NPI *Secondary outcomes*: • NPI-D
Homma *et al.*, 2000[44]	*Design*: RCT, double-blind, multicentre *Interventions*: 1. donepezil 5 mg/day 2. placebo *Number of centres*: 54 *Duration of treatment*: 24 weeks *Sponsor*: not reported	*Inclusion criteria*: DSM-IV criteria for AD; CDR 1 or 2; MMSE 10–26; ADAS-J cog score of ≥ 15 *Numbers*: 268 participants randomised (ITT, $n = 263$). 1. 134 to 5 mg/day 2. 129 to placebo 228 protocol-compatible patients reported: donepezil $n = 116$, placebo $n = 112$ *Mean age ± SD (range)*: 1. 70.1 ± 7.6 (52–83) 2. 69.4 ± 8.8 (48–90)	*Primary outcomes*: • ADAS-Jcog (Japanese ADAS-cog) • J-CGIC (Japanese CGIC) *Secondary outcomes*: • CDR-SB • MENFIS • CMCS • Adverse events
Krishnan *et al.*, 2003[45]	*Design*: RCT, double-blind, multicentre *Interventions*: 1. donepezil, 5 mg/day for the first 28 days, 10 mg/day thereafter 2. Placebo *Number of centres*: 3 *Duration of treatment*: 24 weeks *Sponsor*: Eisai and Pfizer	*Inclusion criteria*: ≥ 50 years with a diagnosis of probable, mild-to-moderate, uncomplicated AD according to DSM-IV and NINCDS criteria; CDR of 1or 2; MMSE of 10–26; Hachinski score of ≤ 4 *Numbers*: 1. $n = 34$ to donepezil 2. $n = 33$ to placebo *Mean age ± SD*: 1. 74.4 ± 7.0 2. 72.4 ± 10.1	*Primary outcomes*: • Brain *N*-acetylaspartate concentrations *Secondary outcomes*: • ADAS-cog • Adverse events
Mohs *et al.*, 2001[46]	*Design*: RCT, double-blind, multicentre *Interventions*: 1. 5 mg/day donepezil (28 days), 10 mg/day thereafter, up to 54 weeks 2. placebo *Number of centres*: 31 *Duration of treatment*: 54 weeks *Sponsor*: Eisai and Pfizer	*Inclusion criteria*: probable AD (DSM-IV and NINCDS) and MMSE score of 12–20; CDR score of 1 or 2 and modified Hachinski ischaemia scores of ≤ 4 at both screening and baseline. Participants also required to perform 8 of 10 instrumental ADL (each score ≤ 2) and 5 of 6 basic ADL (each score ≤ 2) on the ADFACS at both screening and baseline *Numbers*: 1. 214 to donepezil 2. 217 to placebo *Mean age ± SD*: 1. 75.4 (0.6), 50–91 2. 75.3 (0.6), 49–94	*Primary outcomes*: • Alzheimer's Disease Functional Assessment and Change Scale (adapted for the study) (ADFACS) • CDR • MMSE *Secondary outcomes*: • Adverse events

continued

TABLE 3 *Characteristics of included studies for donepezil (cont'd)*

Study	Methods	Participants	Outcomes
Nunez *et al.*, 2003[48]	*Design*: RCT, multicentre *Interventions*: 1. 10 mg/day donepezil 2. placebo *Number of centres*: not stated *Duration of treatment*: 12 weeks *Sponsor*: not reported	*Inclusion criteria*: mild to moderate (MMSE 10–26) possible or probable AD (NINCDS-ADRDA, DSM-IV). Patients entered an open-label donepezil phase before randomisation; those showing 'no apparent clinical benefit' were then randomised to study groups. Numbers: 202 randomised 1. 99 to 10 mg/day donepezil 2. 103 to placebo *Mean age ± SD*: 1. 74.1 ± 7.6 2. 71.4 ± 9.3	*Primary outcomes*: • MMSE • ADAS-cog • DAD • NPI
Rogers *et al.*, 1998[51]	*Design*: RCT, double-blind, multicentre *Interventions*: 1. 5 mg/day donepezil 2. 10 mg/day donepezil (blinded forced titration phase – 5 mg was given for the first 7 days) 3. placebo *Number of centres*: 20 *Duration of treatment*: 24 weeks *Sponsor*: Eisai (USA) and Eisai (Japan)	*Inclusion criteria*: ≥ 50 years old; probable AD by NINCDS-ADRDA criteria, DSM-III-R categories of 290.00 or 290.10; MMSE 10–26; CDR of 1 or 2 *Numbers*: 473 randomised 1. 154 to 5 mg/day 2. 157 to 10 mg/day 3. 162 to placebo *Mean age ± SE (range)*: 1. 72.9 ± 0.6 (51–86) 2. 74.6 ± 0.6* (53–94) 3. 72.6 ± 0.6 (56–88) * $p = 0.03$	*Primary outcomes*: • ADAS-cog • CIBIC-plus *Secondary outcomes*: • MMSE • CDR-SB • Patient-rated QoL • Adverse events
Rogers *et al.*, 1998[52]	*Design*: RCT, double-blind, multicentre *Interventions*: 1. 5 mg/day donepezil 2. 10 mg/day donepezil (blinded forced titration phase – 5 mg was given for the first 7 days) 3. placebo *Number of centres*: 23 *Duration of treatment*: 12 weeks *Sponsor*: Eisai (USA) and Eisai (Japan)	*Inclusion criteria*: ≥ 50 years; probable AD by NINCDS-ADRDA criteria, DSM-III-R categories of 290.00 or 290.10; MMSE 10–26; CDR of 1 or 2 *Numbers*: 468 randomised 1. 157 to 5 mg/day 2. 158 to 10 mg/day 3. 153 to placebo *Mean age ± SE (range)*: 1. 73.8 ± 0.67 (50–94) 2. 73.4 ± 0.65 (50–92) 3. 74.0 ± 0.65 (52–93)	*Primary outcomes*: • ADAS-cog • CIBIC-plus *Secondary outcomes*: • MMSE • CDR-SB • Patient-rated QoL • Adverse events
Rogers *et al.*, 1996[53]	*Design*: multicentre, double-blind, parallel group RCT *Interventions*: 1. 1 mg donepezil 2. 3 mg donepezil 3. 5 mg donepezil 4. placebo *Number of centres*: not reported, but 10 members of the donepezil study group are listed, all at different locations *Duration of treatment*: 12 weeks *Sponsor*: Eisai (USA) and Eisai (Japan)	*Inclusion criteria*: 55–85 years; mild to moderately severe AD (DSM-III-R and NINCDS criteria); MMSE 10–26; CDR 1 or 2 *Numbers*: 161 randomised 1. 42 to 1 mg donepezil 2. 40 to 3 mg donepezil 3. 39 to 5 mg donepezil 4. 40 to placebo *Mean age (range)*: 1. 72.6 (55–85) 2. 71.0 (54–85) 3. 72.9 (55–85) 4. 70.6 (56–84)	*Primary outcomes*: • ADAS-cog. • CGIC *Secondary outcomes*: • ADL • MMSE • CDR-SB • QoL-P, QoL-C • Adverse events

continued

TABLE 3 *Characteristics of included studies for donepezil (cont'd)*

Study	Methods	Participants	Outcomes
Seltzer *et al.*, 2004[55]	*Design*: RCT, double-blind, multicentre *Interventions*: 1. donepezil 5 mg/day for 6 weeks and then 10 mg/day 2. placebo *Number of centres*: 17 *Duration of treatment*: 24 weeks *Sponsor*: Pfizer and Eisai	*Inclusion criteria*: 50–90 years; **[Commercial/academic confidential information removed]**; MMSE 21–26 *Numbers*: 153 patients randomised 1. 96 to donepezil 10 mg/day 2. 57 to placebo *Mean age ± SD (range)*: **[Commercial/academic confidential information removed]**	*Primary outcomes*: • Modified ADAS-cog. *Secondary outcomes*: • CDR-SB • MMSE • Computerised Memory Battery • **[Commercial/academic confidential information removed]** • Apathy Scale • PGA • Compliance • Adverse events
Winblad *et al.*, 2001;[47] Wimo *et al.*, 2003[56]	*Design*: RCT, double-blind, multicentre *Interventions*: 1. donepezil 5 mg/day for 28 days and then 10 mg/day 2. placebo *Number of centres*: 28 *Duration of treatment*: 52 weeks *Sponsor*: Pfizer Pharmaceuticals Group, Pfizer	*Inclusion criteria*: possible or probable AD on DSM-IV and NINCDS-ADRDA; MMSE 10–26 *Numbers*: 286 patients randomised 1. 142 to donepezil 5 mg/day 2. 144 to placebo *Mean age ± SE (range)*: 1. 72.1 ± 8.6 (49–86) 2. 72.9 ± 8.0 (51–88)	*Primary outcomes*: • Gottfries-Bråne–Steen (GBS) scale. *Secondary outcomes*: • MMSE • PDS • NPI • GDS Wimo *et al.*:[56] IADL scale; Physical Self-maintenance Scale (PSMS)

TABLE 4 *Quality assessment table for donepezil*

Study	Randomisation	Concealment of allocation	Baseline characteristics	Eligibility	Blinding of assessors	Care provider blinding	Patient blinding	Reporting outcomes	ITT analysis	Withdrawals explained
AD2000[43]	Ad	Un	Rep	Ad	Par	Ad	Ad	In	In	Ad
Burns *et al.*, 1999[50]	Un	Un	Rep	Ad	Par	Par	Par	Ad	In	Ad
Gauthier *et al.*, 2002[41]	Un	Un	Rep	Par	Un	Un	Un	In	In	Par
Greenberg *et al.*, 2000[54]	Ad	Ad	Rep	Ad	Ad	Ad	Ad	Ad	In	Ad
Holmes *et al.*, 2004[49]	Ad	Ad	Rep	Ad	Un	Ad	Ad	Ad	In	Ad
Homma *et al.*, 2000[44]	Un	Un	Rep	Ad	Un	Par	Par	Ad	In	Par
Krishnan *et al.*, 2003[45]	Ad	Un	Rep	Ad	Un	Ad	Ad	In	In	Par
Mohs *et al.*, 2001[46]	Un	Un	Rep	Ad	Ad	Par	Par	Par	In	Ad
Nunez *et al.*, 2003[48]	Un	Un	Rep	Ad	Un	Par	Par	In	In	Un
Rogers *et al.*, 1998[51]	Ad	Un	Rep	Ad	Par	Par	Par	Ad	In	Par
Rogers *et al.*, 1998[52]	Un	Un	Rep	Ad	Ad	Par	Par	Ad	In	Ad
Rogers *et al.*, 1996[53]	Un	Un	Rep	Ad	Un	Par	Par	Par	In	Ad
[Commercial/academic confidential information relating to Seltzer *et al.*[55] removed]										
Winblad *et al.*, 2001[47,56]	Ad	Un	Rep	Ad	Un	Par	Par	Ad	In	Ad

Ad, adequate; In, inadequate; Par, partial; Rep, reported; Un, unknown.

particularly important when using subjective outcome measures.

Seven studies adequately reported the point estimates and measures of variability for all outcomes; however, none of these included an appropriate ITT analysis. All studies state that an ITT analysis was undertaken; however, this was defined as being on all participants randomised to treatment who received at least one dose of medication and who had baseline and at least one post-baseline assessment of efficacy (LOCF). In each case some participants were missing from the analysis as they did not have at least one post-baseline assessment, and therefore these studies were judged to have inadequate ITT analysis.

All but one study[48] gives details of the numbers of withdrawals from the study; however, four do not give reasons for withdrawal.

[Commercial/academic confidential information relating to Seltzer and colleagues[55] removed]

Assessment of effectiveness

Cognitive outcomes

ADAS-cog

Seven parallel RCTs and one crossover RCT report the ADAS-cog (Homma and colleagues[44] use a Japanese version) and results are given in *Table 5*. Results in this table are ordered by the number of comparison groups and then alphabetically: the results from the trials with two comparisons are shown first followed by the trials with three and four comparisons. Results for the crossover study were presented in several different ways, for groups A and B, for all who received placebo (whether in A or B) and similarly for all who received donepezil, for those who completed both parts of the crossover and for whom no data points were missing. In the current review only data reported in terms of donepezil treatment versus placebo treatment (therefore treated as a parallel comparison) are discussed. The 'ITT' (LOCF) results are presented unless not reported in an individual trial. These conventions will apply throughout the report. One trial only reported the treatment difference and the statistical significance value without any data and has therefore been omitted from this table.[48] In this and later tables, values estimated from figures are given in italics.

On the ADAS-cog a negative mean change indicates a clinical improvement.

Three trials were two-arm comparisons, three were three-arm trials and one was a four-arm trial.

Changes from baseline scores for each individual trial are given in *Table 5*. The summary that follows will predominantly discuss comparisons between 5 mg donepezil and placebo and between 10 mg donepezil and placebo, regardless of the number of arms in the individual trial. The one study[45] where the intervention dose of donepezil was 5 mg/day for 28 days followed by 10 mg/day until study completion will be treated as having a 10 mg/day dose.

Donepezil 5 mg/day versus placebo. Six trials included an intervention group with a daily dose of 5 mg donepezil. The mean change from baseline ADAS-cog score was between –2.43 and 0.2 for the donepezil group and between 0.11 and 3.2 for the placebo groups. Some of this variation may be explained by differences in the sample sizes, length of follow-up and study quality. Sample sizes ranged from 103 in the study by Greenberg and colleagues[54] to 545 in the two relevant groups in Burns and colleagues' comparison.[50] Length of follow-up was 24 weeks in five studies and 12 weeks in two studies.[52,53] No studies reported an adequate ITT analysis, and only Greenberg and colleagues[54] were rated as having adequate randomisation and concealment of allocation procedures. Blinding of outcome assessors was only adequate in two studies[52,54] and blinding of care provider and participants was rated as being adequate in only one study.[54] Baseline ADAS-cog scores were similar between trials. The mean treatment difference in change from baseline scores between donepezil and placebo was ~0.90. Overall, all studies found that ADAS-cog scores were statistically significantly lower (better) with 5 mg donepezil per day than placebo.

Three of the six studies provided data (mean change and standard deviation) that allowed them to be combined in a meta-analysis (*Figure 1*). Pooling the data using a fixed-effect model showed an overall improvement in ADAS-cog with 5 mg/day donepezil compared with placebo [WMD –2.51 (95% CI: –3.26 to –1.76)]. Heterogeneity was not significant at $p = 1$. No difference was noted using a random-effects model.

Donepezil 10 mg/day versus placebo. Four trials included an intervention group with a daily dose of 10 mg donepezil. The mean change from baseline ADAS-cog score was between –2.7 and 0.2 for the donepezil group and between 0.4 and 3.2 for the placebo groups. Some of this variation may be explained by differences in the sample sizes which range from 66 in the study by Krishnan and

TABLE 5 *ADAS-cog for donepezil*

Greenberg *et al.*, 2000[54] Change in ADAS-cog mean ± SEM				
Donepezil 5 mg/day (*n* = 51)	**Placebo (*n* = 52)**			***p*-Value versus placebo**
–1.50 ± 0.58	0.62 ± 0.61			Not reported
Homma *et al.*, 2000[44] JADAS-cog mean change from baseline ± SE				
Donepezil 5 mg/day (*n* = 134)	**Placebo (*n* = 129)**			***p*-Value versus placebo**
–2.43 ± 0.45, *n* = 126	0.11 ± 0.49, *n* = 113			$p = 0.001$
Krishnan *et al.*, 2003[45] Change from baseline *Numbers estimated from figure*				
Donepezil 10 mg/day (*n* = 34)	**Placebo (*n* = 32)**			***p*-Value versus placebo**
0.2	*3.2*			$p < 0.04$
Burns *et al.*, 1999[50] Least-squares mean change from baseline *Numbers estimated from figure*				
1. Donepezil 5 mg/day (*n* = 271)	**2. Donepezil 10 mg/day (*n* = 273)**	**3. Placebo (*n* = 274)**		***p*-Value versus placebo**
0.2	*–1.2*	*1.7*		1. $p = 0.0021$ 2. $p < 0.0001$
Rogers *et al.*, 1998[51] Mean change from baseline ± SEM				
1. Donepezil 5 mg/day (*n* = 152)	**2. Donepezil 10 mg/day (*n* = 150)**	**3. Placebo (*n* = 153)**		***p*-Value versus placebo**
–0.67 ± 0.51	–1.06 ± 0.51	1.82 ± 0.49		1. $p < 0.0001$ 2. $p < 0.0001$
Rogers *et al.*, 1998[52] Least-squares mean change from baseline ± SEM				
1. Donepezil 5 mg/day (*n* = 156)	**2. Donepezil 10 mg/day (*n* = 155)**	**3. Placebo (*n* = 150)**		***p*-Value versus placebo**
–2.1 ± 0.43	–2.7 ± 0.43	0.4 ± 0.43		1. $p < 0.001$ 2. $p < 0.001$
Rogers *et al.*, 1996[53] Mean change from baseline ± SE *Numbers estimated from figure*				
1. Donepezil 1 mg/day (*n* = 42)	**2. Donepezil 3 mg/day (*n* = 40)**	**3. Donepezil 5 mg/day (*n* = 39)**	**4. Placebo (*n* = 40)**	***p*-Value versus placebo**
–0.9	*–1.4*	*–2.5*	*0.7*	3. $p < 0.003$
Rogers *et al.*, 1996[53] Adjusted mean (min., max.) change from baseline				
1. Donepezil 1 mg/day (*n* = 42)	**2. Donepezil 3 mg/day (*n* = 40)**	**3. Donepezil 5 mg/day (*n* = 39)**	**4. Placebo (*n* = 40)**	***p*-Value versus placebo**
–0.9 (–11.3, 12.0)	–1.4 (–12.0, 11.0)	–2.5 (–8.0, 7.0)	0.7 (–7.0, 14.5)	1. $p = 0.105$ 2. $p = 0.036$ 3. $p = 0.002$

colleagues[45] to 547 in the two relevant groups in Burns and colleagues' comparison.[50] Study quality also differed between studies; no studies were rated as having both adequate randomisation and concealment of allocation procedures, blinding of outcome assessors was only adequate in one trial[52] and blinding of care provider and participants was rated as only being adequate in one study.[45] The primary outcome in one trial[45] was brain *N*-acetylaspartate concentrations and therefore this study may not have been powered for changes in the ADAS-cog. The length of follow-up was 24 weeks in all but one study (12 weeks).[52] Baseline ADAS-cog scores were similar between trials. The mean treatment difference in change from baseline scores between donepezil and placebo was approximately 2.97 points. Overall, all four studies found that ADAS-cog scores were statistically significantly lower (better) with 10 mg/day donepezil than placebo.

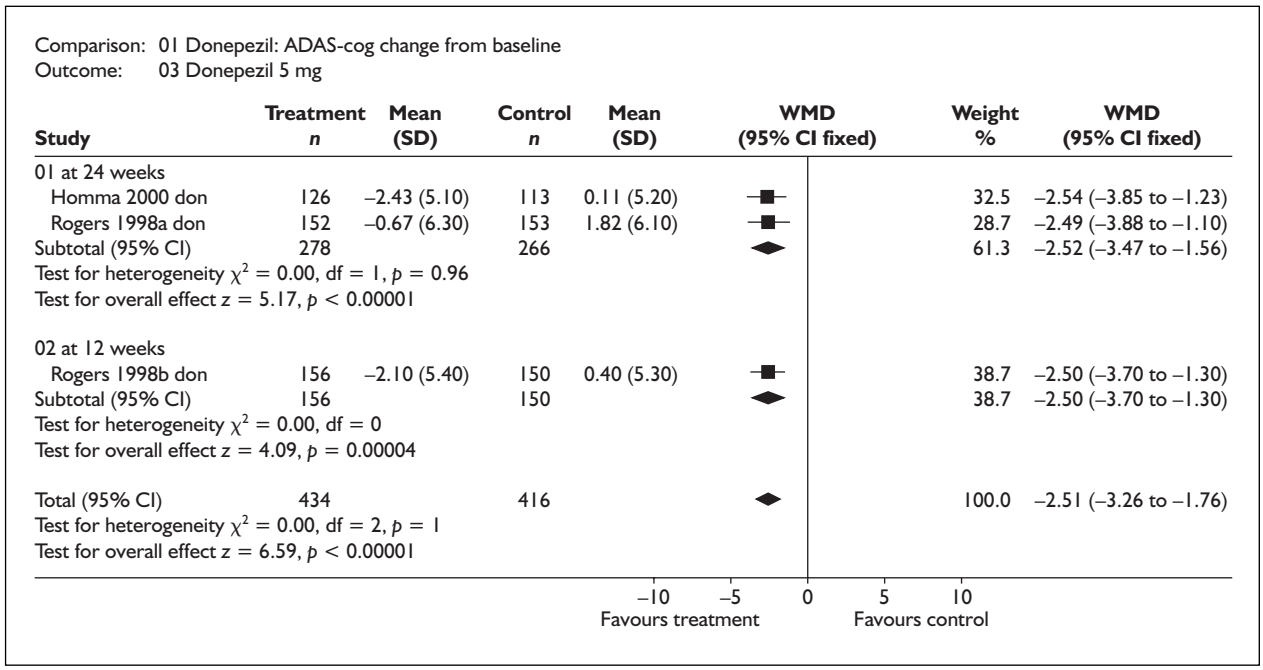

FIGURE 1 *ADAS-cog change from baseline with donepezil 5 mg*

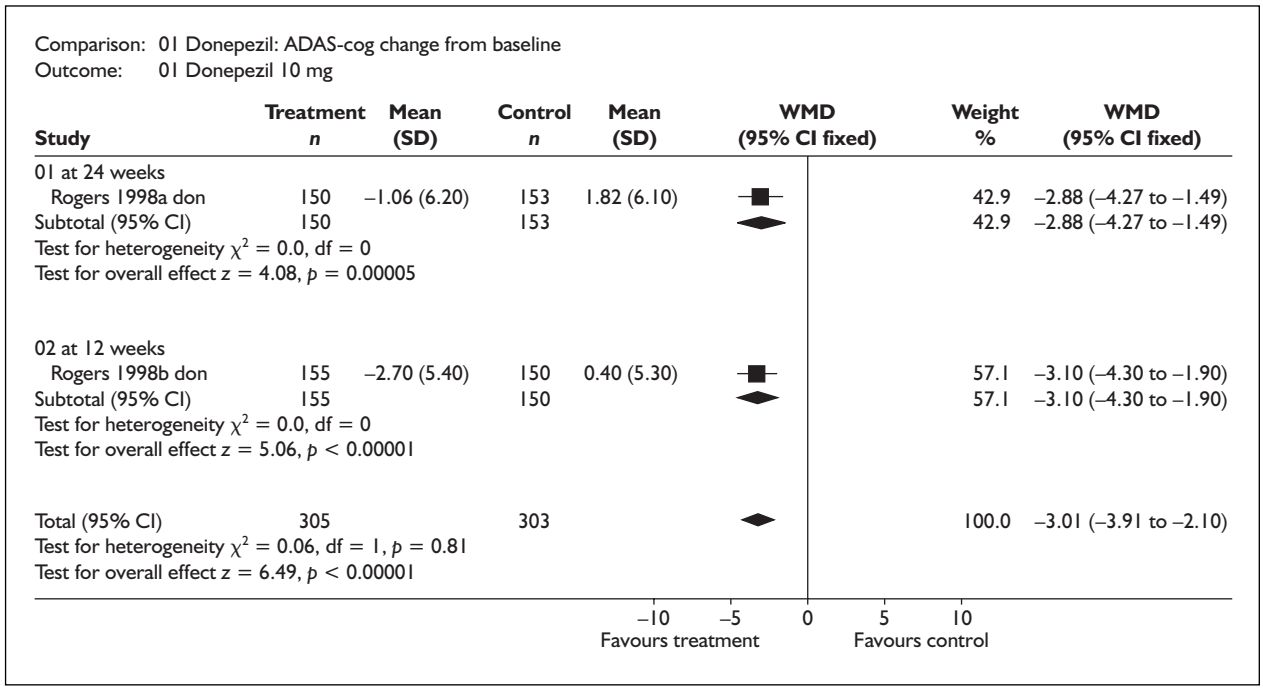

FIGURE 2 *ADAS-cog change from baseline with donepezil 10 mg*

Two of the four studies provided data (mean change and standard deviation) that allowed them to be combined in a meta-analysis (*Figure 2*). Pooling the data using a fixed-effect model showed an overall improvement in ADAS-cog with 10 mg/day donepezil compared with placebo [WMD –3.01 (95% CI: –3.91 to –2.10)]. Heterogeneity was not significant at $p = 0.81$. No difference was noted using a random-effects model.

One unpublished trial of mild AD participants reported mean change on a modified ADAS-cog scale.[55] Those in the 10 mg donepezil group ($n = 91$) demonstrated a mean change in

ADAS-cog of –1.7 (SEM 0.45) and those in the placebo group (n = 55) a mean change in ADAS-cog of 0.6 (SEM 0.57). The study demonstrated a statistically significant difference, p = 0.001. The mean mADAS-cog at baseline was 23.8 (SEM 0.85) in the donepezil group and 24.1 (SEM 0.93) in the placebo group.

Cognitive responders on ADAS-cog

One study reported data on 'cognitive responders'.[51] Cognitive responders were defined as those with at least a 4-point improvement on the ADAS-cog; they also presented data on those with at least a 7-point improvement. In this study 37.8% of participants given 5 mg donepezil and 53.5% of participants given 10 mg donepezil had at least a 4-point improvement. These compare with 26.8% of those participants given the placebo intervention. Participants with at least a 7-point improvement on ADAS-cog were 15.4 and 25.2% in the two donepezil groups (5 and 10 mg/day, respectively) compared with 7.8% in the placebo group. The trial also reports that the percentage of participants with poorer ADAS-cog scores from baseline were 20.3% in the 5 mg donepezil group, 18.9% in the 10 mg donepezil group and 42.3% in the placebo group, hence cognitive worsening was higher in those treated with placebo. No statistical analyses were undertaken to compare differences in any of the groups' responses on these outcomes.

MMSE

Nine included trials report the MMSE and results are given in *Table 6*. On the MMSE a positive mean change indicates a clinical improvement.

Six trials were two-arm comparisons, two were three-arm trials and one was a four-arm trial. Change from baseline score for each trial is given in *Table 6*. The summary that follows will predominantly discuss comparisons between 5 mg donepezil and placebo and 10 mg donepezil and placebo, regardless of the number of arms in the individual trial. The two studies[41,47] where the intervention dose of donepezil was 5 mg/day for 28 days followed by 10 mg/day until study completion will be treated as having a 10 mg/day dose. The one trial where participants received either 5 or 10 mg donepezil is reported separately. The one trial that had 12 weeks of open-label treatment prior to randomisation is also reported separately.[49]

Donepezil 5 mg/day versus placebo. Three trials included an intervention group with a daily dose of 5 mg donepezil. The mean change from baseline MMSE was between 0.24 and 2.0 for the donepezil group and between –0.97 and 1.2 for the placebo groups. The mean treatment difference in change from baseline scores between donepezil and placebo was ~1 point. Overall, all studies demonstrated improvement in MMSE in the donepezil groups compared with the placebo groups, although these differences reached statistical significance in only two.[51,52] Some of the variation between trials may be due to sample size as the one trial that did not reach statistical significance had small sample sizes. There may also be differences attributed to the properties of the scale (see discussion in Chapter 10).

Two of the three studies provided data (mean change and standard deviation) that allowed them to be combined in a meta-analysis (*Figure 3*). Pooling the data using a fixed-effects model showed an overall improvement in MMSE with 5 mg/day donepezil compared with placebo [WMD 1.08 (95% CI: 0.57 to 1.58)]. Heterogeneity was not statistically significant, p = 0.63. No difference was noted using a random-effects model.

Donepezil 10 mg/day versus placebo. Six trials included an intervention group with a daily dose of 10 mg donepezil. The mean change from baseline MMSE was between –0.46 and 1.7 for the donepezil group and between –2.18 and 0.5 for the placebo groups. This variation may in part be explained by differences in the study duration, with longer duration reducing the mean change MMSE score from baseline. Baseline MMSE scores were generally similar between these trials. The mean treatment difference in change from baseline scores between donepezil and placebo was ~1.5 points. Overall, all studies demonstrated statistically significant improvement in MMSE in the donepezil groups compared with the placebo groups.

Two of the six studies provided data (mean change and standard deviation) that allowed them to be combined in a meta-analysis (*Figure 4*). Pooling the data using a fixed-effect model showed an overall improvement in MMSE with 10 mg/day donepezil compared with placebo [WMD 1.30 (95% CI: 0.78 to 1.82)]. Heterogeneity was not statistically significant, p = 0.85. No difference was noted using a random-effects model.

In one study, the dose of donepezil was 5 or 10 mg/day, with approximately half receiving each dose.[43] The reported MMSE change from baseline in the donepezil-treated group at 60 weeks was –1.5. The reported MMSE change from baseline in the placebo group at 60 weeks was –1.75.

TABLE 6 *MMSE for donepezil*

AD2000 2004[43] Change from baseline *Numbers estimated from figure*			
Donepezil 5 mg/day or 10 mg/day (*n* = 154)	**Placebo (*n* = 160)**		***p*-Value versus placebo**
–1.5	*–1.75*		Not reported[a]
Gauthier *et al*., 2002[41] Standardised MMSE least-squares mean change from baseline *Numbers estimated from figure*			
Donepezil 10 mg/day (*n* = 91)	**Placebo (*n* = 100)**		***p*-Value versus placebo**
1.5	*–0.56*		0.0002
Holmes *et al*., 2004[49] Mean change from baseline ± SEM			
Donepezil 10 mg/day (*n* = 41)	**Placebo (*n* = 55)**		***p*-Value versus placebo**
–0.1 (0.6)	–1.8 (0.5)		$p = 0.02$
Mohs *et al*., 2001[46] Adjusted mean change from baseline *Numbers estimated from figure*			
Donepezil 10 mg/day (*n* = 207)	**Placebo (*n* = 208)**		***p*-Value versus placebo**
0.6 (n = *207)*	*–0.6* (n = *208)*		$p < 0.001$
Nunez *et al*., 2003[48] Least-squares mean change from baseline *Numbers estimated from figure*			
Donepezil 10 mg/day (*n* = 99)	**Placebo (*n* = 103)**		***p*-Value versus placebo**
1.7	*0.5*		$p < 0.05$
Winblad *et al*., 2001[47] Wimo *et al*., 2003[56] Least-squares mean change from baseline ± SE *Numbers estimated from figure*			
Donepezil 10 mg/day (*n* = 142)	**Placebo (*n* = 144)**		***p*-Value versus placebo**
–0.46 ± 0.34 (n = *135)*	*–2.18 ± 0.29* (n = *137)*		$p < 0.001$
Rogers *et al*., 1998[51] Mean change from baseline ± SE			
1. Donepezil 5 mg/day (*n* = 153)	**2. Donepezil 10 mg/day (*n* = 150)**	**3. Placebo (*n* = 154)**	***p*-Value versus placebo**
0.24 ± 0.29	0.39 ± 0.29	–0.97 ± 0.28	1. $p = 0.0007$ 2. $p = 0.0002$
Rogers *et al*., 1998[52] Least-squares mean change from baseline ± SEM			
1. Donepezil 5 mg/day (*n* = 156)	**2. Donepezil 10 mg/day (*n* = 156)**	**3. Placebo (*n* = 150)**	***p*-Value versus placebo**
1.0 ± 0.25	1.3 ± 0.24	0.04 ± 0.25	1. $p < 0.004$ 2. $p < 0.001$
Rogers *et al*., 1996[53] Adjusted mean (min., max.) change from baseline			
1. Donepezil 1 mg/day (*n* = 42)	**2. Donepezil 3 mg/day (*n* = 40)**	**3. Donepezil 5 mg/day (*n* = 39)**	**4. Placebo (*n* = 40)**	***p*-Value versus placebo**
0.6 (–4.0, 7.0)	0.9 (–7.0, 5.0)	2.0 (–1.0, 7.0) $p < 0.05$ relative to 1 mg	1.2 (–6.0, 8.0)	Not reported
Rogers *et al*., 1996[53] Mean change from baseline *Numbers estimated from figure*			
1. Donepezil 1 mg/day (*n* = 42)	**2. Donepezil 3 mg/day (*n* = 40)**	**3. Donepezil 5 mg/day (*n* = 39)**	**4. Placebo (*n* = 40)**	***p*-Value versus placebo**
0.66	*0.80*	*2.00*	*1.37*	Not reported

[a] *p*-Values were reported for the overall treatment effect ($p < 0.0001$) rather than for the difference between groups at this particular time point (60 weeks).

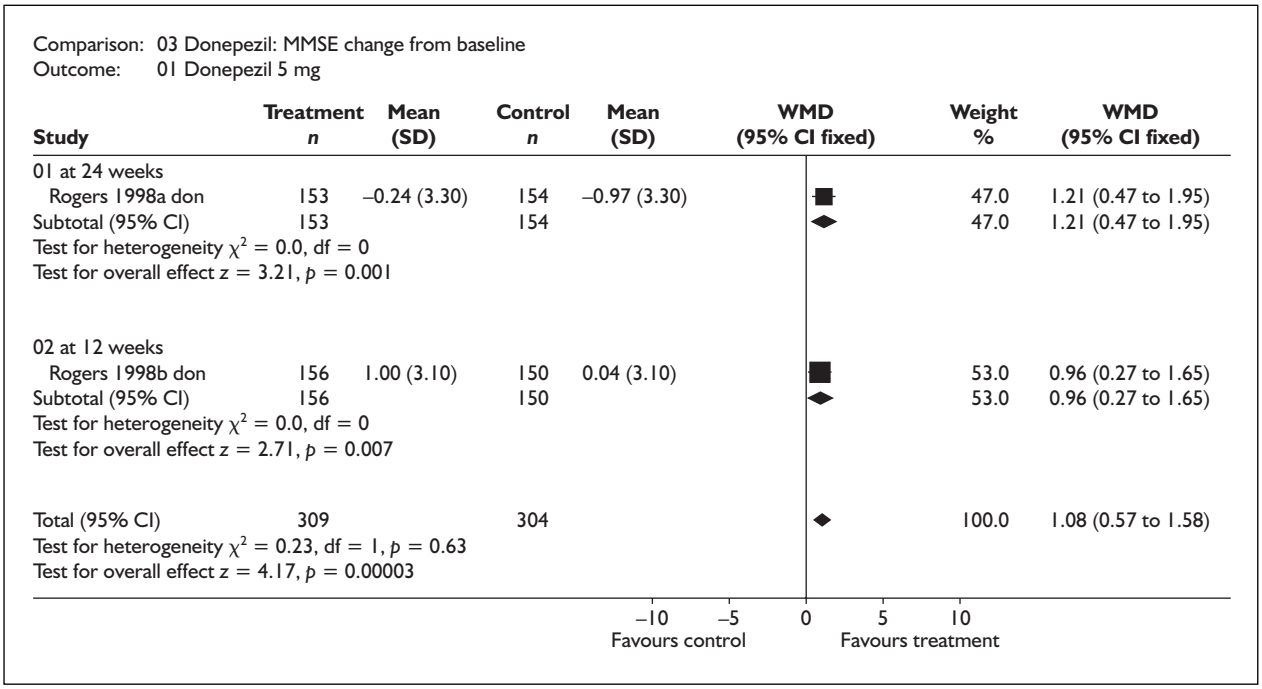

FIGURE 3 *MMSE change from baseline with donepezil 5 mg*

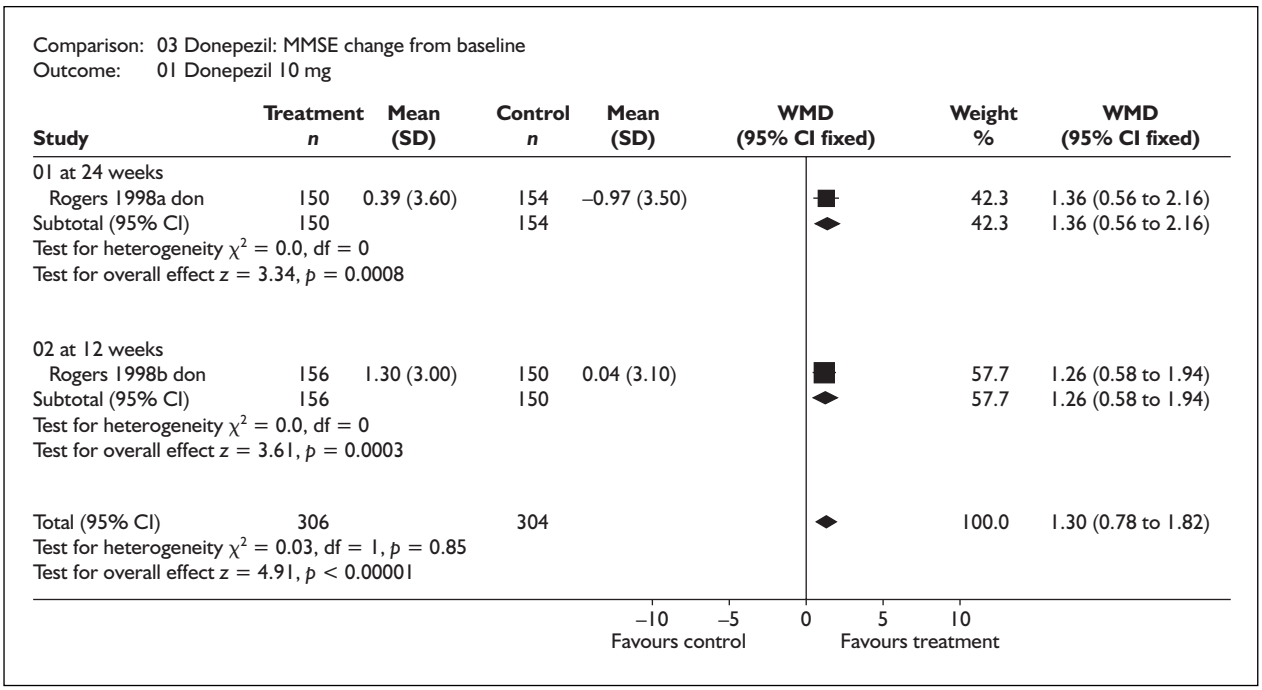

FIGURE 4 *MMSE change from baseline with donepezil 10 mg*

Although both groups showed a decline in MMSE, this decline was seen to be greater in the placebo group. One other trial[49] that had a 12-week prerandomisation open-label treatment period demonstrated a mean change from randomisation at 24 weeks of –0.1 (SEM 0.6) in the 10 mg donepezil group and –1.8 (SEM 0.5) in the placebo groups. This was statistically significant at $p = 0.02$.

One unpublished trial[55] reported mean change in MMSE score over 24 weeks. The participants in this study were those with mild AD; the mean MMSE at baseline was 24.1 (SEM 0.18) in the

donepezil group and 24.3 (SEM 0.18) in the placebo group. Those in the 10 mg donepezil group (n = 91) demonstrated a mean change in MMSE of 1.4 (SEM 0.33) and those in the placebo group (n = 55) a mean change in MMSE of 0.1 (SEM 0.41). The study demonstrated a statistically significant difference, p = 0.002.

SIB

One included trial[41] reports data on the Severe Impairment Battery (SIB), which is a measure of cognition where positive scores indicate clinical improvement. In this 24-week trial cognition was demonstrated to be improved compared with baseline: the mean change from baseline was 1.4 in those treated with 10 mg donepezil and –3.0 in those treated with placebo. This difference (4.4 points) was statistically significant at $p < 0.01$.

Computerised Memory Battery

One unpublished 24-week trial[55] reports on the Computerised Memory Battery (CMB), which is designed to simulate critical cognitive tasks of everyday life. No details of the properties of this scale were presented; however, from the results it can be inferred that a positive score relates to improvement. **[Commercial/academic confidential information removed]** CMB facial recognition showed a mean change of 0.8 (SEM 0.64) and –1.6 (SEM 0.75) in the donepezil and placebo groups, respectively, p = 0.007. The methods in the report also suggest that other components were tested (name–face association total acquisition, house/object placement task (total and first), telephone number recall, 10 and seven digits), but data for these are not presented.

Summary: treatment with donepezil appears to confer an improvement on measures of cognition when compared with placebo and this effect is mirrored in the meta-analysis.

Global outcomes

CIBIC-plus/CGIC

Four RCTs report the Clinician's Interviews-based Impression of Change-plus (CIBIC-plus)[41,50–52] and three trials report the Clinical Global Impression of Change (CGIC)[44,53,54] (Homma and colleagues[44] use a Japanese version) and can be seen in *Tables 7* and *8*. The CIBIC-plus/CGIC use a seven-point Likert-type scale where 1 = marked improvement, 4 = no change and 7 = marked worsening.

TABLE 7 *CGIC for donepezil*

Homma et *al.*, 2000[44] JCGIC		
Donepezil 5 mg/day (n = 134) (1 unassessable)	**Placebo (n = 129) (1 unassessable)**	***p*-Value versus placebo**
Improvement rates (% slightly improved or better): 52% Aggravation rates (% slightly aggravated or worse): 17%	Improvement rates (% slightly improved or better): 22% Aggravation rates (% slightly aggravated or worse): 43%	
N, (%) change: Markedly improved: 1 (1) Improved: 21 (16) Slightly improved: 42 (31) No change: 44 (33) Slightly aggravated: 19 (14) Aggravated: 6 (4) Markedly aggravated: 0 (0)	*N*, (%) change: Markedly improved: 2 (2) Improved: 13 (10) Slightly improved: 10 (8) No change: 49 (38) Slightly aggravated: 22 (17) Aggravated: 25 (19) Markedly aggravated: 1 (1)	p = 0.001
Greenberg *et al.*, 2000[54] No. (%)		
Donepezil 5 mg/day	**Placebo**	***p*-Value versus placebo**
Improved/total 12/51 (24) Worsened/total 14/51 (27)	Improved/total 12/53 (23) Worsened/total 19/53 (36)	p = 0.34

Rogers *et al.*, 1996[53] CGIC at endpoint [success (5–7)/failure (1–4)]				
1. Donepezil 1 mg/day (n = 42)	**2. Donepezil 3 mg/day (n = 40)**	**3. Donepezil 5 mg/day (n = 39)**	**4. Placebo (n = 40)**	***p*-Value versus placebo**
34 (82%)/7 (18%)	33 (83%)/7 (18%)	34 (90%)/4 (11%)	32 (80%)/8 (20%)	3. p = 0.039

Three trials[41,44,54] were two-arm comparisons, three were three-arm comparisons[50–52] and one was a four-arm comparison.[53] Change from baseline scores for each individual trial can be seen in *Tables 7* and *8*. The summary that follows will predominantly discuss comparisons between 5 mg donepezil and placebo and 10 mg donepezil and placebo, regardless of the number of arms in the individual trial. The one study[41] where the intervention dose of donepezil was 5 mg/day for 28 days followed by 10 mg/day until study completion will be treated as having a 10 mg/day dose.

Donepezil 5 mg/day versus placebo. Six trials included an intervention group with a daily dose

TABLE 8 *CIBIC-plus for donepezil*

Gauthier *et al.*, 2002[41] CIBIC-plus least-squares mean scores *Numbers estimated from figure*			
Donepezil 10 mg/day (*n* = 98)	**Placebo (*n* = 105)**		***p*-Value versus placebo**
4.0	*4.5*		$p = 0.0003$
Gauthier *et al.*, 2002[41] % participants rated as improved or no change (≤4)			
Donepezil 10 mg/day (*n* = 98)	**Placebo (*n* = 105)**		***p*-Value versus placebo**
70%	47%		$p = 0.0007$
Burns *et al.*, 1999[50] Mean change from baseline ± SE *Numbers estimated from figures*			
1. Donepezil 5 mg/day (*n* = 271)	**2. Donepezil 10 mg/day (*n* = 273)**	**3. Placebo (*n* = 274)**	***p*-Value versus placebo**
4.23 ± 0.06	*4.13 ± 0.06*	*4.52 ± 0.06*	1. $p = 0.0072$ 2. $p < 0.0002$
Burns *et al.*, 1999[50] % participants rated as improved (CIBIC-plus scores ≤3 at endpoint)			
1. Donepezil 5 mg/day (*n* = 271)	**2. Donepezil 10 mg/day (*n* = 273)**	**3. Placebo (*n* = 274)**	***p*-Value versus placebo**
21	25	14	Not reported
Burns *et al.*, 1999[50] % treatment failures (CIBIC-plus scores ≥5 at endpoint)			
1. Donepezil 5 mg/day (*n* = 271)	**2. Donepezil 10 mg/day (*n* = 273)**	**3. Placebo (*n* = 274)**	***p*-Value versus placebo**
43	37	51	Not reported
Rogers *et al.*, 1998[51] Mean change from baseline ± SE			
1. Donepezil 5 mg/day (*n* = 149)	**2. Donepezil 10 mg/day (*n* = 149)**	**3. Placebo (*n* = 152)**	***p*-Value versus placebo**
4.15 ± 0.09	4.07 ± 0.07	4.51 ± 0.08	1. $p = 0.0047$ 2. $p < 0.0001$
Rogers *et al.*, 1998[51] % participants rated as 'improved' (CIBIC-plus scores ≤3)			
1. Donepezil 5 mg/day (*n* = 149)	**2. Donepezil 10 mg/day (*n* = 149)**	**3. Placebo (*n* = 152)**	***p*-Value versus placebo**
26	25	11	
Rogers *et al.*, 1998[52] Least-squares mean ± SEM change			
1. Donepezil 5 mg/day (*n* = 156)	**2. Donepezil 10 mg/day (*n* = 155)**	**3. Placebo (*n* = 150)**	***p*-Value versus placebo**
3.9 ± 0.08	3.8 ± 0.08	4.2 ± 0.07	1. $p = 0.03$ 2. $p = 0.08$
Rogers *et al.*, 1998[52] % participants rated as 'improved' (CIBIC-plus scores ≤3)			
1. Donepezil 5 mg/day (*n* = 156)	**2. Donepezil 10 mg/day (*n* = 155)**	**3. Placebo (*n* = 150)**	***p*-Value versus placebo**
32	38	18	

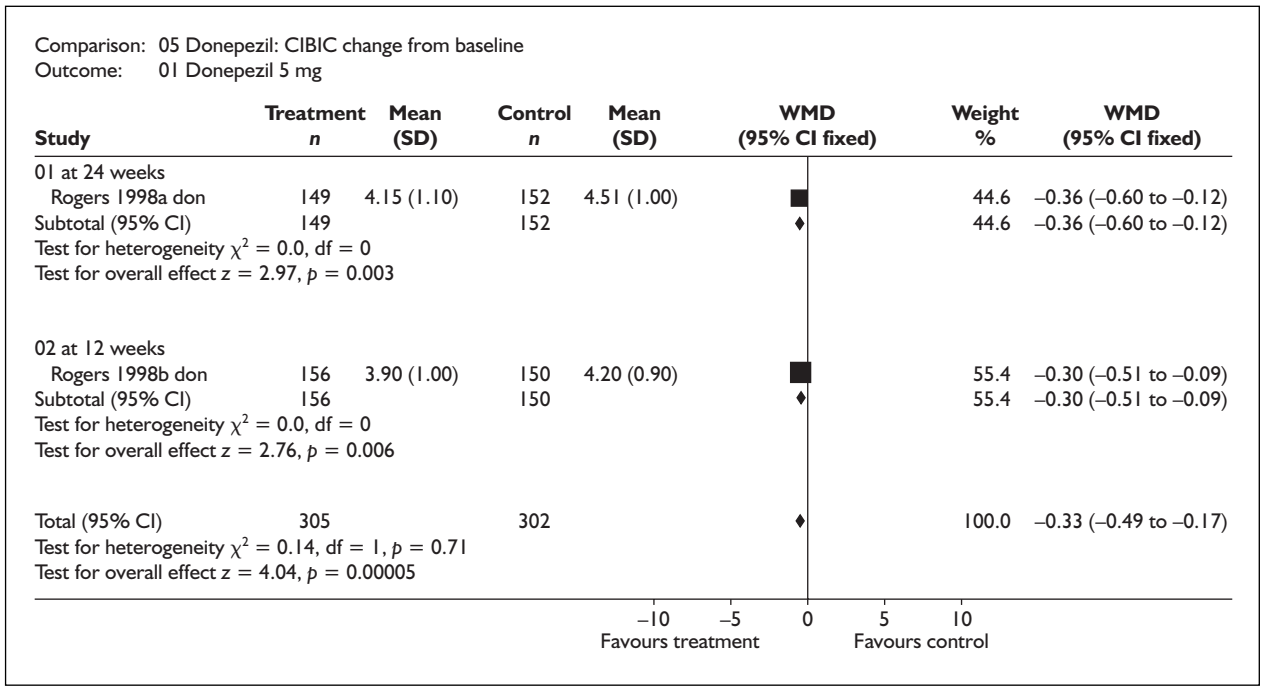

FIGURE 5 *CIBIC-plus change from baseline with donepezil 5 mg*

of 5 mg donepezil; however, only those reporting the CIBIC-plus (three trials[50–52]) report data in terms of mean change from baseline. Data on the CGIC were reported in terms of proportions responding and are discussed below. The mean change from baseline CIBIC-plus score was between 3.9 and 4.23 for the donepezil group and between 4.2 and 4.52 for the placebo groups. Despite variations between the study sample sizes, the quality of the studies and the length of duration of the studies, there is little variation in the scores between studies. This is likely to reflect the nature of the measure, which is non-parametric, of a non-interval nature and has just seven items on the scale. Overall, all three studies found that CIBIC-plus scores were statistically significantly lower (better) with 5 mg/day donepezil than placebo.

Two of the three studies provided data (mean change and SD) that allowed them to be combined in a meta-analysis (*Figure 5*). Pooling the data using a fixed-effect model showed an overall improvement in CIBIC-plus with 5 mg/day donepezil compared with placebo [WMD –0.33 (95% CI: –0.49 to –0.17)]. Heterogeneity was not significant, $p = 0.71$. No difference was noted using a random-effects model.

Donepezil 10 mg/day versus placebo. Four trials included an intervention group with a daily dose of 10 mg donepezil. The mean change from baseline CIBIC-plus score was between 3.8 and 4.13 for the donepezil group and between 4.2 and 4.52 for the placebo groups. Overall all four studies found that CIBIC-plus scores were statistically significantly lower (better) with 10 mg/day donepezil than placebo.

Two of the four trials provided data (mean change and SD) that allowed them to be combined in a meta-analysis (*Figure 6*). Pooling the data using a fixed-effect model showed an overall improvement in CIBIC-plus with 5 mg/day donepezil compared with placebo [WMD –0.42 (95% CI: –0.57 to –0.27)]. Heterogeneity was not statistically significant, $p = 0.8$. No difference was noted using a random-effects model.

CIBIC-plus/CGIC responders

Seven included trials report data on global 'responders', demonstrating clinical improvement on the CIBIC-plus/CGIC. Three trials reporting the CIBIC-plus and one reporting the CGIC classify responders as those with scores of ≤ 3.[44,50–52] One trial reporting the CGIC[53] and one trial reporting the CIBIC-plus rate treatment success as scores 1–4 (which includes no change),[41] whereas one other does not report the definition used.[54] Regardless of the definition used, in each trial the proportion of responders was higher in the treatment groups than the placebo groups, but these differences were not tested for statistical significance, except in two trials.[41,54] One of these

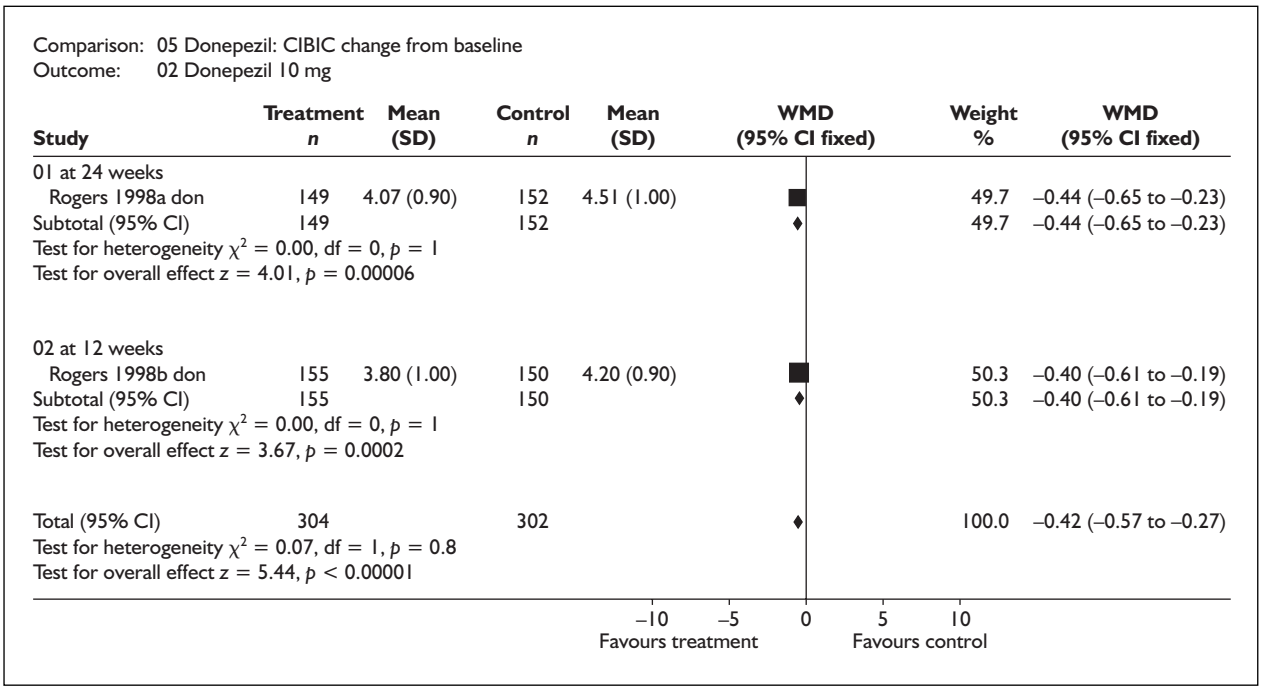

FIGURE 6 *CIBIC-plus change from baseline with donepezil 10 mg*

demonstrated a statistically significant difference,[41] whereas the other demonstrated no statistically significant difference.[54] The proportion showing clinical improvement in the studies using the conventional cut-off ≤ 3 ranged from 21 to 32% in the 5 mg donepezil groups, 25 to 38% in the 10 mg donepezil groups and 11 to 24% in the placebo groups. One study[53] reporting treatment success (scores 1–4) demonstrated a 90% success rate in their 5 mg donepezil treatment group compared with an 80% success rate in the placebo group. The remaining study[41] reporting treatment success as scores 1–4 demonstrated a 70% success rate in their 10 mg donepezil-treated group compared with a 47% success rate in the placebo group. All but two of these studies were of 24 weeks' duration; the study of Rogers and colleagues[52,53] were of 12 weeks' duration.

Three studies provided data for 5 mg/day donepezil compared with placebo that allowed them to be combined in a meta-analysis (*Figure 7*). Pooling the data using a fixed-effect model showed an overall improvement in CIBIC-plus responders with donepezil compared with placebo [odds ratio (OR) 2.83 (95% CI: 2.04 to 3.93)]. Heterogeneity was not statistically significant, $p = 0.35$. No difference was noted using a random-effects model.

Two studies provided data for 10 mg/day donepezil compared with placebo that allowed them to be combined in a meta-analysis (*Figure 8*). Pooling the data using a fixed-effect model showed an overall improvement in CIBIC-plus responders with donepezil compared with placebo [OR 2.72 (95% CI: 1.82 to 4.08)]. Heterogeneity was not statistically significant, $p = 0.88$. No difference was noted using a random-effects model.

CDR-SB

Five trials included the CDR-SB and the results are given in *Table 9*. On the CDR-SB a negative score indicates clinical improvement.

One trial was a two-arm comparison, three were three-arm trials and one was a four-arm trial. Changes from baseline scores for each individual trial can be seen in *Table 9*. The summary that follows will predominantly discuss comparisons between 5 mg donepezil and placebo and between 10 mg donepezil and placebo, regardless of the number of arms in the individual trial.

Donepezil 5 mg/day versus placebo. Four trials included an intervention group with a daily dose of 5 mg donepezil. The mean change from baseline CDR-SB score was between –0.11 and 0.06 for the donepezil group and between –0.14 and 0.75 for the placebo groups. Overall changes from baseline were small, which is likely to be related to the scoring of the scale. The differences between donepezil and placebo groups were

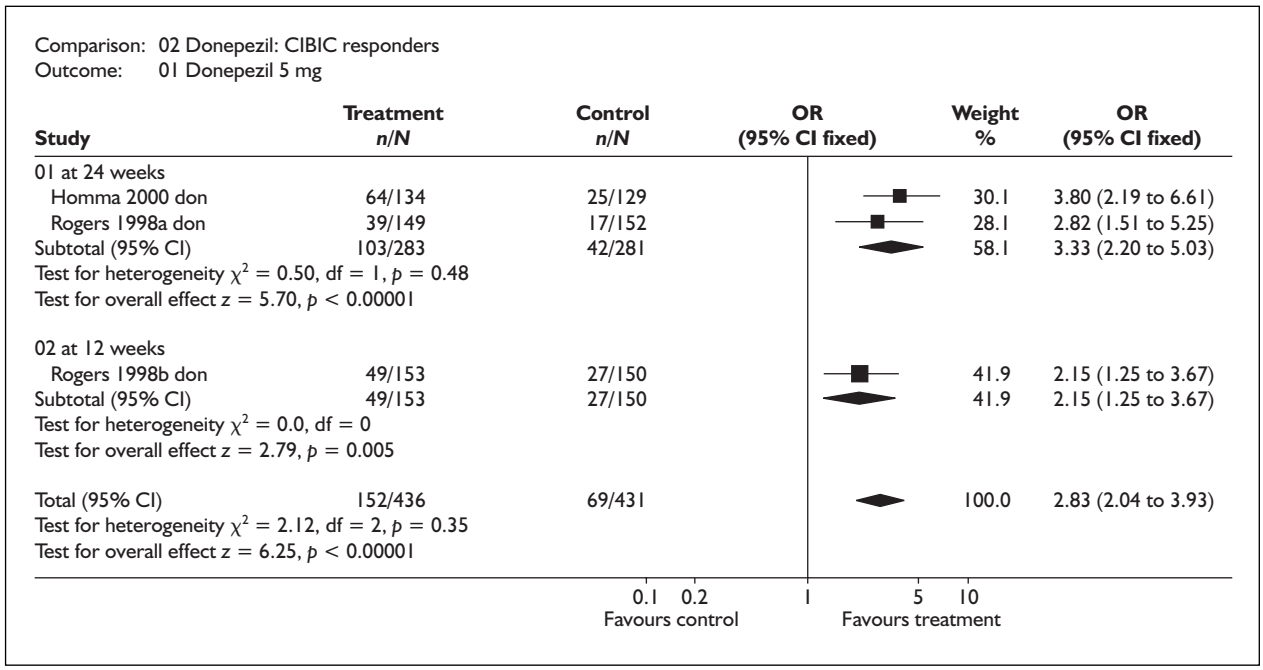

FIGURE 7 *CIBIC-plus responders with donepezil 5 mg*

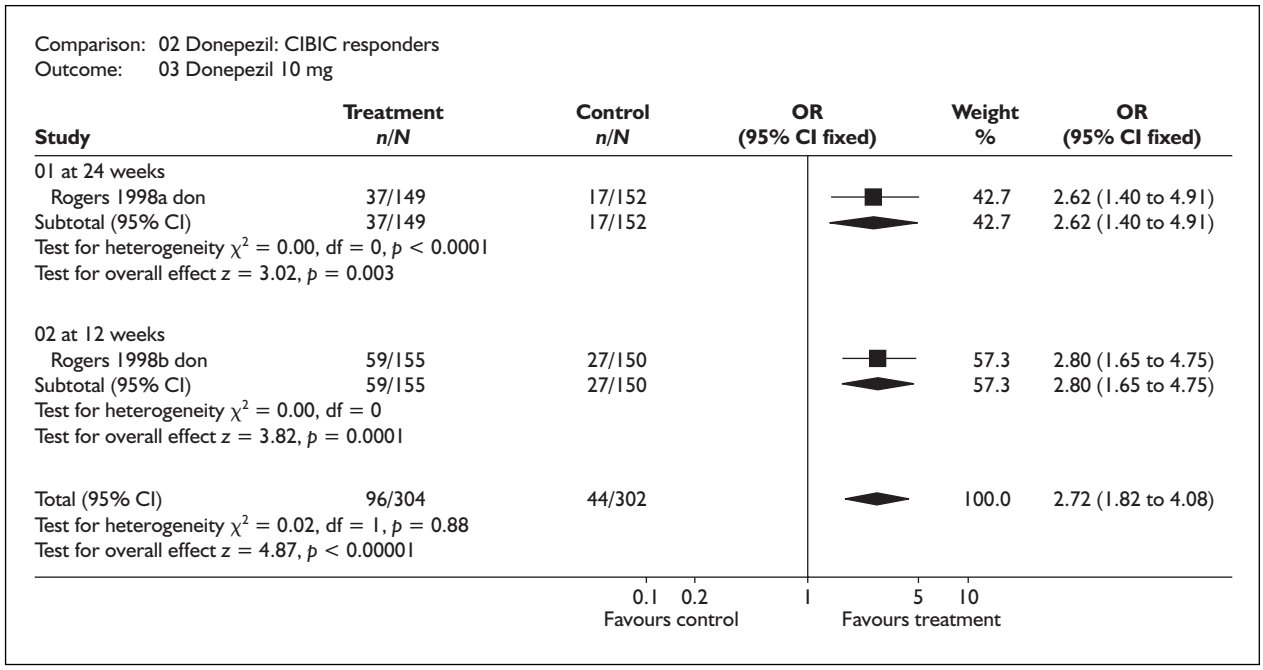

FIGURE 8 *CIBIC-plus responders with donepezil 10 mg*

statistically significant in three studies.[44,50,51] Two studies showed no overall difference between the study groups.

Two of the four trials provided data (mean change and SD) that allowed them to be combined in a meta-analysis (*Figure 9*). Pooling the data using a fixed-effect model showed no overall improvement on the CDR with 5 mg/day donepezil compared with placebo [WMD –0.22 (95% CI: –0.46 to 0.03)]. There was, however, statistically significant heterogeneity (χ^2 test for heterogeneity 6.27, df = 1, $p = 0.012$). No difference was noted using a random-effects model.

TABLE 9 *CDR-SB for donepezil*

Homma *et al.*, 2000[44] Mean change ± SE from baseline (NB: protocol compatible population)			
Donepezil 5 mg/day (*n* = 116)	**Placebo (*n* = 112)**		***p*-Value versus placebo**
–0.10 ± 0.12	0.75 ± 0.15		$p = 0.001$
Burns *et al.*, 1999[50] Least-squares mean change from baseline ± SE *Numbers estimated from figures*			
1. Donepezil 5 mg/day (*n* = 271)	**2. Donepezil 10 mg/day (*n* = 273)**	**3. Placebo (*n* = 274)**	***p*-Value versus placebo**
0.06 ± 0.11	*–0.06 ± 0.11*	*0.37 ± 0.06*	1. $p = 0.0344$ 2. $p = 0.0033$
Rogers *et al.*, 1998[51] Mean change from baseline ± SEM			
1. Donepezil 5 mg/day (*n* = 154)	**2. Donepezil 10 mg/day (*n* = 151)**	**3. Placebo (*n* = 153)**	***p*-Value versus placebo**
–0.01 ± 0.14	–0.02 ± 0.14	0.58 ± 0.14	1. $p = 0.0008$ 2. $p = 0.0007$
Rogers *et al.*, 1998[52] Least-squares mean ± SEM change from baseline			
1. Donepezil 5 mg/day (*n* = 156)	**2. Donepezil 10 mg/day (*n* = 154)**	**3. Placebo (*n* = 150)**	***p*-Value versus placebo**
–0.10 ± 0.11	–0.31 ± 0.11	–0.14 ± 0.11	1. $p = 0.32$

Rogers *et al.*, 1996[53] Adjusted mean (min., max.) change from baseline				
1. Donepezil 1 mg/day (*n* = 42)	**2. Donepezil 3 mg/day (*n* = 40)**	**3. Donepezil 5 mg/day (*n* = 39)**	**4. Placebo (*n* = 40)**	***p*-Value versus placebo**
0.18 (–2.0, 5.0)	0.23 (–3.0, 6.0)	–0.11 (–2.0, 3.0)	0.10 (–2.0, 3.0)	Not reported
Rogers *et al.*, 1996[53] Mean change from baseline				
1. Donepezil 1 mg/day (*n* = 42)	**2. Donepezil 3 mg/day (*n* = 40)**	**3. Donepezil 5 mg/day (*n* = 39)**	**4. Placebo (*n* = 40)**	***p*-Value versus placebo**
0.10	0.04	–0.15	0.04	Not reported

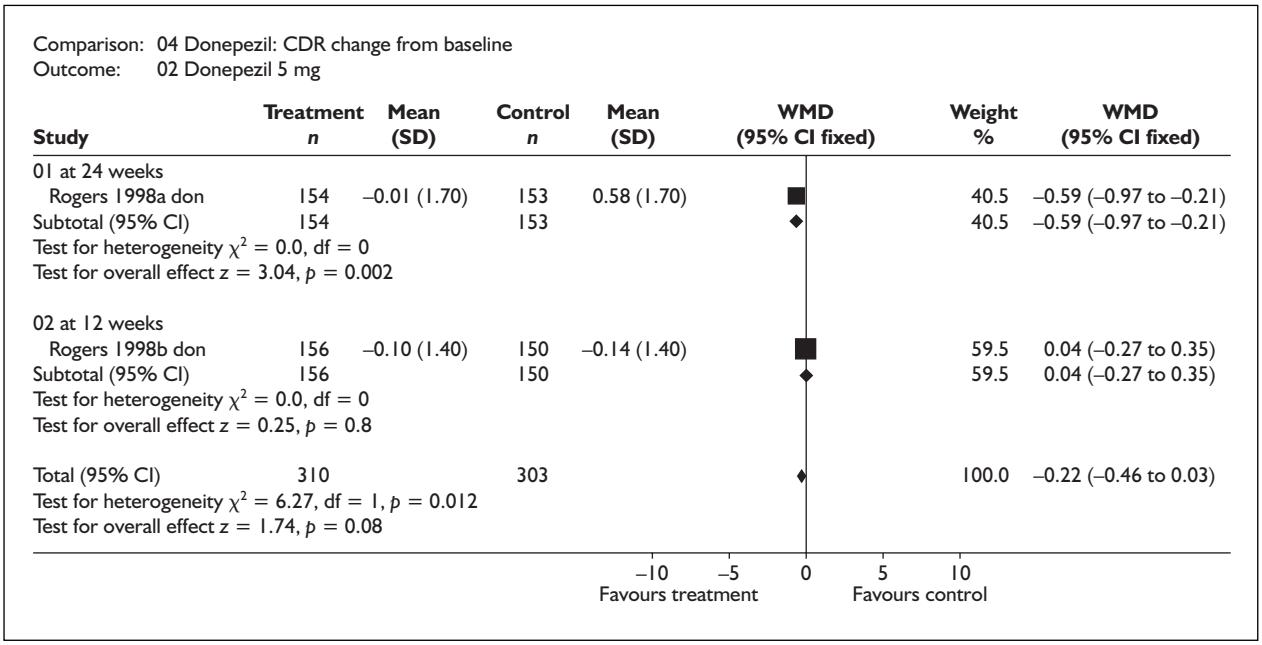

FIGURE 9 *CDR change from baseline with donepezil 5 mg*

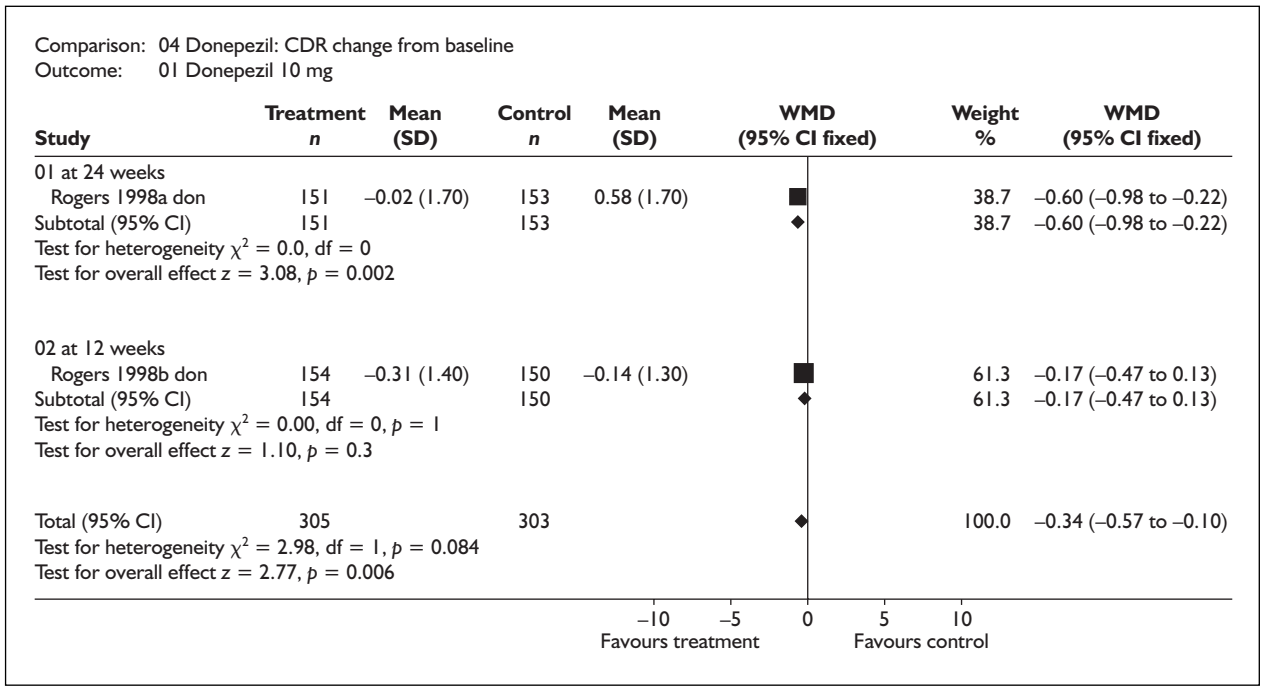

FIGURE 10 *CDR change from baseline with donepezil 10 mg*

Donepezil 10 mg/day versus placebo. Three trials included an intervention group with a daily dose of 10 mg donepezil. The mean change from baseline CDR-SB score was between –0.31 and –0.02 for the donepezil group and between –0.14 and 0.58 for the placebo groups. Overall, two studies found that CDR-SB scores were statistically significantly lower (better) with 10 mg/day donepezil than placebo. One study showed a reduction in CDR-SB that was greater in the donepezil than the placebo group but the difference was not statistically significant.[52]

Two of the three trials provided data (mean change and SD) that allowed them to be combined in a meta-analysis (*Figure 10*). Pooling the data using a fixed-effect model showed an overall improvement on the CDR with 10 mg/day donepezil compared with placebo [WMD –0.34 (95% CI: –0.57 to –0.10)]. However, there was statistically significant heterogeneity (χ^2 test for heterogeneity 2.98, df = 1, $p = 0.084$). With a random-effects model the data suggest no improvement for 10 mg/day donepezil compared with placebo [WMD –0.37 (95% CI: –0.79 to 0.05)].

One unpublished study also collected data on the CDR-SB; however, data are not presented in the document received. The study reports that data were not statistically significant in this population with mild AD.[55]

GBS

The Gottfries–Bråne–Steen (GBS) scale was used as a global measure in one trial.[47] The GBS has a range of 0–62 where a higher score relates to clinical deterioration. At 52 weeks the GBS mean change score was smaller in donepezil-treated participants compared with placebo-treated participants but this difference was not statistically significant ($p = 0.054$). The mean (± SEM) change score was 8.0 ± 1.4 in the 10 mg donepezil-treated group and 11.5 ± 1.6 in the placebo group. The proportion 'improved' from baseline was 31.2 versus 21.6% in the donepezil versus placebo groups, respectively.

GDS

One trial reported data on the Global Deterioration Scale (GDS).[47] On this scale, a negative change in score relates to clinical improvement. At 52 weeks the GDS mean change (± SEM) score was better in donepezil-treated participants than placebo-treated participants: 0.25 ± 0.06 in the 10 mg donepezil treated group and 0.44 ± 0.06 in the placebo group, $p < 0.05$. The proportion 'improved' from baseline was 14 versus 5% in the donepezil versus placebo groups, respectively, $p < 0.05$.

MENFIS

The Mental Function Impairment Scale (MENFIS) was used in one trial[44] and is a modification of the

GBS prepared by the study authors for a previous study. Scores range from 0 to 78 and the higher the score the greater the degree of the deficit. In this trial, the mean change (± SEM) from baseline was statistically significantly lower (better) in the 5 mg donepezil group than the placebo group: –0.72 ± 0.53 donepezil, 1.84 ± 0.69 placebo, $p < 0.05$.

PGA
One unpublished study[55] reports the Patient Global Assessment scale (PGA).
[Commercial/academic confidential information removed]

Summary: on measures of global outcomes, treatment with donepezil generally leads to more favourable results when compared with treatment with placebo.

Functional outcomes
Eight included trials report data on activities of daily living (ADL) scales; each reporting on different scales.

Unified ADL
Rogers and colleagues[53] report on the Unified Activities of Daily Living (ADL) assessment scale where a negative response relates to improvement. This trial was a four-arm comparison of three daily doses of donepezil (1, 3 and 5 mg) and placebo.[53] Full details can be seen in Appendix 7; however, for consistency the discussion that follows will concentrate on the 5 mg donepezil group versus placebo. At 12 weeks of follow-up the mean (adjusted) change from baseline favoured the 5 mg donepezil group compared with the placebo group, although this difference does not reach statistical significance (–3.1 versus 1.5, donepezil 5 mg/day versus placebo, respectively, $p = 0.068$).

PDS
Winblad and colleagues[47] report on the PDS where a positive score indicates clinical improvement. This trial had an intervention dose of donepezil of 5 mg/day for 28 days followed by 10 mg/day until study completion and will be treated as having a 10 mg/day dose. Mean change from baseline for overall activities of daily living at 52 weeks of follow-up was –10.8 in the 10 mg donepezil group and –15.3 in the placebo group. This difference (4.5 points) was statistically significant at $p < 0.05$. Full details of changes in individual items can be found in Appendix 7. Individual items on the PDS that also reached statistical significance from placebo were self-care ($p < 0.05$), memory ($p < 0.01$), and telephone ($p < 0.01$), although it is unclear whether corrections for multiple comparisons were made to the level for statistical significance.

IADL
In a subsequent publication of additional outcomes from the Winblad[47] trial, data on the proportion deteriorating on the Instrumental ADL (IADL) scale was also reported.[56] The study reports that overall, statistically significantly fewer participants in the donepezil group (10 mg) deteriorated in individual IADL items at week 52 compared with placebo, $p < 0.05$. The overall proportions are not presented, but the proportion deteriorating on individual items can be found in Appendix 7.

ADFACS
One study assessed function with the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS), which they adapted for the study (see Appendix 7).[46] This scale has a range of 0–54, where lower scores correspond to better function. The adjusted mean change from baseline to the 54-week endpoint was 2.4 in the donepezil and 3.85 in the placebo group. This difference (1.45 points) was statistically significant, showing better function in the donepezil-treated group ($p < 0.001$).

IDDD
A modified Interview for Deterioration in Daily Living in Dementia (IDDD) scale was used in one trial (see Appendix 7).[50] On this scale, a value of 68 was the boundary between clinical improvement or decline, where a value <68 indicates clinical improvement and a value >68 clinical decline. In this 24-week study, mean change (± SEM) in baseline scores on the IDDD were 70.4 ± 0.4 in the 5 mg/day donepezil group, 69.4 ± 0.4 in the 10 mg/day donepezil group and 71.1 ± 0.4 in the placebo groups. The difference between the 10 mg/day donepezil group and placebo was statistically significant ($p < 0.01$).

CMCS
One 24-week study included the Caregiver-rated Modified Crichton Scale (CMCS), which is a modified Crichton Geriatric Rating Scale (CGRS).[44] On this scale, a minus change score relates to clinical improvement. The mean change ± SEM from baseline was 1.03 ± 0.66 in the donepezil-treated group (5 mg/day) compared with 3.45 ± 0.71 in the placebo-treated group. This shows that both groups deteriorated but the degree of deterioration was less in the donepezil group than the placebo group. The difference between the groups was statistically significant ($p = 0.01$). Full details can be found in Appendix 7.

DAD
The Disability Assessment for Dementia (DAD) scale was used to assess function in two trials;[41,48] on the DAD a positive score indicates clinical improvement. Data can be found in Appendix 7. One study[48] does not present full data on this outcome; it reports that the difference between the 10 mg donepezil group and the placebo group was –3.67 and that there was no statistically significant difference between groups, $p = 0.11$. The other study reporting the DAD[41] demonstrated no mean change from baseline at 24 weeks in the 10 mg donepezil group and a –9.5 point mean change in the placebo group at 24 weeks; the difference between these groups was statistically significant at $p < 0.001$.

BADLS
One study[43] used the Bristol Activities of Daily Living (BADLS) score, comparing those treated with donepezil 5 or 10 mg with placebo. Results are reported for 60 weeks of follow-up (estimated from figures), where the donepezil-treated participants ($n = 157$) had a mean change of –5 points and the placebo treated participants ($n = 150$) a mean change of –6.5.

Rates of institutionalisation
One study[43] reports differences between donepezil- and placebo-treated participants in rates of institutionalisation. These were 9 versus 14% in the two groups, respectively, at 1 year; this comparison was not statistically significant.

Time to loss of ADL, institutional care or both
One study[43] monitored the time to loss of ADL (defined as loss of either two or four basic or six of 11 instrumental activities on the BADLS) and/or time to institutional care. This study showed that after 1 year of follow-up the proportion was 13% in the donepezil-treated group and 19% in the placebo group. These rates were demonstrated to be not statistically significantly different, $p = 0.3$.

Summary: better functional ability in donepezil-treated participants is generally observed when compared with placebo using a variety of different measures of ADL, although this is not always statistically significant. Over the longer term there may be little difference between participants treated with donepezil and those treated with placebo.

Quality of life
Three studies report data on patient-rated QoL (QoL is as reported by individual trials and may or may not constitute health-related QoL). None of the rating scales used have been validated for use in dementia and all are generic rather than disease-specific measures so caution is required in the interpretation of the findings. Two studies use a 'patient-rated QoL' scale[51,52] and one used a QoL scale rated by the patient (QoL-P) and one rated by the caregiver (QoL-C); these latter tests were reported to be a well-being score.[53]

On the QoL-P scale, the range of scores was between 0 and 50, where 50 corresponds to best quality. On the QoL-P and QoL-C scales a positive score indicates improvement.

Patient-rated QoL
Both studies were three-arm trials comparing both 5 and 10 mg donepezil treatment with placebo. Mean QoL-P score change from baseline in the 5 mg groups were 11 and 5.7, in the 10 mg groups were 7.5 and –4.3 and in the placebo groups were –2 and 4 in the two trials, respectively.[51,52]

Donepezil 5 mg/day versus placebo. One of the two included studies demonstrated a statistically significant change in baseline score between those treated with 5 mg donepezil and those treated with placebo at 24 weeks[51] demonstrating improved QoL in the 5 mg donepezil-treated group ($p = 0.05$). The other study showed better QoL in the 5 mg donepezil group compared with placebo but this did not reach statistical significance.[52]

Donepezil 10 mg/day versus placebo. One of the two included studies demonstrated a statistically significant change in baseline score between those treated with 10 mg donepezil and those treated with placebo at 12 weeks[52] demonstrating improved QoL in the placebo group ($p = 0.02$) The other study showed better QoL in the donepezil group but this did not reach statistical significance.[51]

QoL-P
In one 12-week study[53] pairwise comparisons of the QoL-P mean change scores between donepezil treatment groups (1, 3 and 5 mg) and the placebo group were shown not to be statistically significant. There was a statistically significant dose–response analysis showing that with increasing doses of donepezil the QoL-P was improved compared with placebo.

QoL-C
In the same 12-week study,[53] pairwise comparisons showed no statistical evidence of improvement over placebo in any of the donepezil groups and no statistically significant dose–response relationship.

Carer mental health and burden
One study measured the psychological well-being of the principal caregiver, as measured by the General Health Questionnaire 30 (GHQ-30). At week 60 the change from baseline score for those caring for people given donepezil (n = 151) was –0.5 and in those caring for people given placebo (n = 153) was similarly –0.5. These are estimated figures.

[Commercial/academic confidential information relating to Seltzer and colleagues[55] removed]

Summary: QoL results show varied results, but this may be related to the measures used and the small number of studies that examined QoL.

Behaviour and mood
The Neuropsychiatric Inventory (NPI) was reported in four trials.[41,43,48,49] The NPI assesses neuropsychiatric disturbances with a 12-item scale based on information from the caregiver. The total score ranges from 0 to 144; on the NPI a negative score indicates clinical improvement. One trial[48] did not report full results on this outcome; the treatment difference between those given 10 mg donepezil compared with those given placebo, after 12 weeks, was 3.16. This difference was reported to be statistically significant at $p < 0.05$. The mean change from baseline score at 24 weeks of 10 mg donepezil in another trial[41] was –5.0 and for placebo 0.92. This difference was statistically significant, $p < 0.01$, suggesting improved behaviour and mood. The trial also reports that individual NPI item analysis at week 24 showed benefit with donepezil compared with placebo on all 12 items of the NPI, with statistically significant differences for delusions (p = 0.0073), apathy (p = 0.0131) and aberrant motor behaviour (p = 0.0232). In another trial,[43] results at 60 weeks showed an NPI change from baseline score of –3 in the 5/10 mg donepezil treatment group (n = 149) compared with –4 in the placebo group (n = 150). The study reports that these differences are not statistically significant. Data have been estimated from figures. One final trial[49] demonstrated a mean change on the NPI from randomisation (after 12 weeks of open-label donepezil) at 24 weeks of –2.9 (SEM 1.6) in the 10 mg donepezil group and 3.3 (SEM 2.1) in the placebo groups. This was statistically significant at p = 0.02. This study also reports data on the Neuropsychiatric Inventory, Distress subscale (NPI-D). Scores at randomisation point at week 12 compared with week 24 also showed improvement (a decrease on the scale) in those treated with 10 mg donepezil compared with those treated with placebo [–1.7 (SEM 0.7) vs 1.1 (SEM 1.1) in the two groups, respectively]. Full details can be found in Appendix 7.

Summary: better behaviour and mood, as assessed by the NPI, are found in participants treated with donepezil than placebo over short to medium durations of follow-up. Over longer periods this difference may be reduced.

Compliance
Compliance was reported to be assessed in four of the 12 published studies. Only one study presented data relating to each study group rather than the total population. In this study, Winblad and colleagues[47] demonstrated a mean overall rate of compliance for the donepezil group of 94.6% and for the placebo group 94.9%. Greenberg and colleagues[54] assessed compliance with dosing by interview of caregivers and pill counts. Based on pills returned, compliance was estimated to be 95.7% for the population evaluated. Homma and colleagues[44] measured compliance by recovery of residual drug from the caregiver on hospital visits every 4 weeks and determining actual number of tablets taken using caregivers' diaries. They note that 98% of the population evaluated reached the specified compliance rate for the efficacy analysis. Rogers and colleagues[52] also measured compliance by counting returned tablets, but no data were presented in the publication as to the rate of compliance.

Compliance was also reported in one unpublished trial.[55] The proportion was calculated by dividing the number of doses by the number of treatment days. In the 10 mg donepezil group the proportion complying was 87.8% (SD 20.3%) and in the placebo group 93.3% (SD 13.6%). **[Commercial/academic confidential information removed]**

Adverse events
Adverse events are especially important in trials because:

- Any evidence of significant adverse events should be taken into account when assessing outcomes relating to treatment response. If treatment response is shown to be beneficial but there are significant adverse events, then the overall benefit would need to be weighed against these occurrences.
- In many cases adverse events are short-lived and not particularly severe. Rare events, which may be more severe, may not be detected in clinical trials with a short duration of treatment. However, all adverse events are recorded in

clinical trials and some comparisons can be made between treatment and placebo groups.
- Some adverse events that occur in the short term and that are obvious to participants and carers have the potential to unblind participants, carers and physicians, even if trials are placebo controlled and participants are not told which treatment they are receiving. Such unblinding could produce biased assessments of treatment effects when the outcomes are self-assessed.
- Some adverse events may lead to discontinuation of a participant in a trial or reduction in the dosage of the treatment. This has the potential to increase the likelihood of bias in the reporting of the outcomes.

Various event rates for selected adverse events were reported in 11 of the included trials and are given in *Table 10*. In general, the quality of reporting of adverse events is variable and is not consistent across trials, with few descriptions of how clinical adverse events were defined. Descriptions of those adverse events that are most commonly reported between the included trials are given here. Severity, where noted, is as reported in each of the individual trials. Very few included studies made statistical comparisons of the rates of adverse events in treatment groups with those in the placebo groups. *Table 11* shows the number of withdrawals due to adverse events.

A range of adverse events were reported in the 11 included studies. One study did not present data for each type of event individually, but rather gave overall incidence rates.[45] Another, a cross-over study, only reported adverse events for all participants receiving donepezil treatment. These studies are not discussed further here but are reported in Appendix 7. Most events presented in the studies were reported as mild or moderate in nature.

Adverse events that were most consistently reported were generally related to the gastrointestinal system.

Nausea and vomiting
Nausea was reported in seven studies.[41,44,46,47,50–52] Rates of nausea in the donepezil groups ranged from around 4 to 24% and in the placebo groups from 1 to 9%. Three included studies report that nausea was statistically significantly greater in those treated with donepezil than those with placebo.[46,50,51] Vomiting was reported in five studies.[41,44,50–52] Rates of vomiting in the donepezil groups ranged from around 1 to 16% and in the placebo groups from 2 to 5%. Two included studies report vomiting incidence that was statistically significantly greater in those treated with donepezil than in those treated with placebo, although in both cases this was only with the higher (10 mg) dose of donepezil.[50,51] Nausea/vomiting was reported in one study, which also showed the same trend with rates being higher in the donepezil treated groups compared to the placebo groups.[53]

Diarrhoea
Diarrhoea was reported in seven studies.[41,44,46,47,50–52] In all studies the incidence of diarrhoea was greater in the donepezil-treated groups, although the magnitude of this difference was less in two studies.[44,47] Three of these seven studies tested the difference in rates statistically and noted significant differences between the groups. Rates of diarrhoea ranged from around 4 to 17% in the donepezil groups and from 3 to 7% in the placebo groups.

Other adverse events that were more consistently reported related to mental and neurological systems.

Headache and dizziness
In six of the included studies rates of headache were reported.[41,44,46,47,52,53] Incidence ranged from around 3 to 13% in the donepezil-treated groups and around 1 to 9% in the placebo-treated groups. No studies report statistically significant differences in the rates of headaches reported between the groups. Dizziness was reported in six studies.[41,47,50–53] In all studies the occurrence of dizziness was greater in the donepezil-treated groups, although the magnitude of this difference was generally small.

Agitation/restlessness
Four included studies reported data on agitation/restlessness.[44,46,52,53] In the donepezil-treated groups this ranged from 0 to 13% and in the placebo-treated groups from 2 to 10%. In general, rates within studies were similar between those in the donepezil-treated group and those in the placebo-treated group. Agitation in participants may, in particular, have an effect on the burden on the caregiver; however, in these studies it would appear that donepezil has a minimal effect on agitation.

Serious adverse events
Rates of 'serious' adverse events were reported in six studies.[41,43,46,47,50,52] In many cases these were classed as being unrelated to the study treatment by assessors; however, in all studies it can be

TABLE 10 *Adverse events for donepezil (note that* p*-values are not reported unless stated)*

AD2000 2004[43] Serious adverse events

Adverse event	**Donepezil 5–10 mg/day (*n* = 242[a])**	**Placebo (*n* = 244[a])**
Serious adverse event	29[b]	23

[a] The time point relating to the reported adverse events is unclear, assumed over the full 3 years.
[b] $p = 0.4$ between groups.

Gauthier *et al.*, 2002[41] Adverse events occurring in ≥5% of participants receiving donepezil: *n* (%)

Adverse event	**Donepezil 10 mg/day (*n* = 102)**	**Placebo (*n* = 107)**
Any adverse event	84 (82.4)	84 (80.0)
Diarrhoea	13 (12.7)	6 (5.7)
Headache	11 (10.8)	4 (3.8)
Respiratory tract infection	11 (10.8)	11 (10.5)
Asthenia	10 (9.8)	5 (4.8)
Arthralgia	9 (8.8)	2 (1.9)
Nausea	8 (7.8)	4 (3.8)
Back pain	8 (7.8)	6 (5.7)
Dizziness	8 (7.8)	4 (3.8)
Weight loss	8 (7.8)	4 (3.8)
Vomiting	7 (6.9)	3 (2.9)
Accidental injury	7 (6.9)	10 (9.5)
Abdominal pain	7 (6.9)	8 (7.6)
Hostility	6 (5.9)	7 (6.7)
Dyspepsia	6 (5.9)	2 (1.0)
Urinary tract infection	6 (5.9)	4 (3.8)

Greenberg *et al.*, 2000[54] Adverse events: *n* (%)

Adverse event	**Donepezil 5 mg/day completers (*n* = 51)**	**Placebo**
Nausea	5 (10)	Not stated
Diarrhoea	3 (6)	
Agitation	3 (6)	

Homma *et al.*, 2000[44] Adverse events: *n* (%)

	Donepezil 5 mg/day (*n* = 136)	**Placebo (*n* = 131) (1 excluded)**
Drug-related incidence	10% (14/136)	8% (10/131)
Total participants with adverse events	54 (40) versus placebo $p = 0.016$	33 (25)
Gastrointestinal disorders		
Diarrhoea	5 (4)	4 (3)
Nausea	6 (4)	1 (1)
Abdominal pain	2 (1)	3 (2)
Vomiting	2 (1)	2 (2)
Anorexia	2 (1)	2 (2)
Constipation	2 (1)	1 (1)
Mental and neurological disorders		
Restlessness	0	3 (2)
Central or peripheral nerve disorders		
Headache	4 (3)	1 (1)
Others		
Cold syndrome	10 (7)[b] versus placebo $p = 0.04$	2 (2)
Inflammation upper airway	3 (2)	2 (2)
Fever	3 (2)	2 (2)
Fracture	1 (1)	3 (2)
Eczema	3 (2)	0

continued

TABLE 10 *Adverse events for donepezil (note that p-values are not reported unless stated) (cont'd)*

Krishnan et *al*., 2003[45]		
	Donepezil 10 mg/day (*n* = 34)	**Placebo (*n* = 32)**
Adverse event	94%	85%

Mohs et *al*., 2001[46] Adverse effects experienced by at least 5% of all participants taking donepezil: *n* (%); severe *n*; related *n*		
	Donepezil 10 mg/day (*n* = 207)	**Placebo (*n* = 208)**
Accidental injury	12 (6); 1; 0	6 (3); 2; 1
Asthenia	14 (7); 1; 8	8 (4); 0; 4
Headache	20 (9); 0; 10	7 (3); 1; 4
Anorexia	12 (6); 0; 9 <0.05[a]	4 (2); 0; 0
Diarrhoea	37 (17); 1; 25 <0.001[a]	11 (5); 0; 9
Dyspepsia	12 (6); 0; 0 <0.05[a]	3 (1); 0; 0
Nausea	19 (9); 0; 14 <0.05[a]	8 (4); 0; 6
Weight loss	13 (6); 0; 11	9 (4); 0; 7
Agitation	28 (13); 1; 13	21 (10); 0; 10
Insomnia	16 (8); 0; 7	7 (3); 0; 3
Rhinitis	25 (12); 1; 5	14 (7); 0; 1
Abrasion	16 (8): 0; 1	7 (3); 0; 0
Urinary tract infection	28 (13); 0; 1 <0.05[a]	14 (7); 0; 0

[a] *p*-Value vs placebo.

Winblad et *al*., 2001,[47] Wimo et *al*., 2003[56] No. of participants with treatment-emergent adverse events that occurred in ≥5% of participants in either treatment group: *n* (%)		
Adverse event	**Donepezil 10 mg/day**	**Placebo**
With adverse event (%)	116 (81.7)	109 (75.7)
Nausea	16 (11.3)	13 (9.0)
Depression	16 (11.3)	11 (7.6)
Anxiety	15 (10.6)	8 (5.6)
Insomnia	14 (9.9)	10 (6.9)
Asthenia	11 (7.7)	5 (3.5)
Headache	11 (7.7)	9 (6.3)
Vertigo	11 (7.7)	3 (2.1)
Diarrhoea	10 (7.0)	10 (6.9)
Syncope	9 (6.3)	4 (2.8)
Bone fracture (accidental)	8 (5.6)	5 (3.5)
Dizziness	9 (6.3)	6 (4.2)
Urinary tract infection	8 (5.6)	10 (6.9)
Constipation	6 (4.2)	9 (6.3)
Confusion	4 (2.8)	9 (6.3)
Hostility	4 (2.8)	8 (5.6)
Abdominal pain	3 (2.1)	8 (5.6)
Of the adverse events, most were:		
Mild	44 (31)	59 (41)
Moderate	5 (31.7)	38 (26.4)

Winblad et *al*., 2001,[47] Wimo et *al*., 2003[56] No. of participants with treatment-emergent serious adverse events that occurred in at least two participants in either treatment group: *n* (%)		
Serious adverse event	**Donepezil 10 mg/day**	**Placebo**
With serious adverse events	35 (24.6)	20 (13.9)
Bone fracture (accidental)	6 (4.2)	3 (2.1))
Syncope	3 (2.1)	1 (0.7)
Headache	3 (2.1)	0
Myocardial infarction	2 (1.4)	1 (0.7)
Nausea	2 (1.4)	1 (0.7)
Urinary tract infection	2 (1.4)	1 (0.7)
Accidental injury	2 (1.4)	0
Pneumonia	2 (1.4)	0
Confusion	1 (0.7)	2 (1.4)
Procedure (medical/surgical/health)	0	2 (1.4)

continued

TABLE 10 *Adverse events for donepezil (note that* p*-values are not reported unless stated) (cont'd)*

Burns *et al.*, 1999[50] Adverse events experienced by at least 5% of all donepezil participants

Adverse event	1. Donepezil 5 mg/day (*n* = 271)	2. Donepezil 10 mg/day (*n* = 273)	3. Placebo (*n* = 274)
Total participants with any adverse event (%)	213 (79)	234 (86)	207 (76)
Digestive system	70 (26) $p \leq 0.05$[a]	127 (47) $p \leq 0.05$[a]	65 (24)
Nausea	7% $p \leq 0.05$[a]	24% $p \leq 0.05$[a]	7%
Diarrhoea	10% $p \leq 0.05$[a]	16% $p \leq 0.05$[a]	4%
Vomiting	4% $p \leq 0.05$[a]	16% $p \leq 0.05$[a]	4%
Anorexia	4%	8%	1%
Nervous system	98 (36) $p \leq 0.05$[a]	109 (40) $p \leq 0.05$[a]	80 (29)
Dizziness	5%	9%	5%
Confusion	7%	6%	6%
Insomnia	7%	8%	4%
Total participants with serious adverse events	19 (7)	29 (11)	25 (9)

[a] *p*-Values versus placebo.

Rogers et al., 1998[51] Adverse events: *n* (%)

Adverse event	1. Donepezil 5 mg/day (*n* = 154)	2. Donepezil 10 mg/day (*n* = 157)	3. Placebo (*n* = 162)
Fatigue	8 (5)	12 (8) $p \leq 0.05$[a]	3 (2)
Diarrhoea	14 (9)	27 (17) $p \leq 0.05$[a]	11 (7)
Nausea	6 (4)	26 (17) $p \leq 0.05$[a]	6 (4)
Vomiting	5 (3)	16 (10) $p \leq 0.05$[a]	3 (2)
Anorexia	3 (2)	11 (7)	3 (2)
Muscle cramps	9 (6)	12 (8) $p \leq 0.05$[a]	1 (1)
Dizziness	15 (10)	13 (8) $p \leq 0.05$[a]	7 (4)
Rhinitis	1 (1)	9 (6)	4 (2)

[a] *p*-Values versus placebo.

Rogers *et al.*, 1998[52] Number (%) with treatment-emergent signs and symptoms (TESS)

Adverse event	Donepezil 5 mg/day (*n* = 157)	Donepezil 10 mg/day (*n* = 158)	Placebo (*n* = 153)
No. with ≥ 1 TESS	106 (68)	124 (78)	106 (69)
Nausea	11 (7)	34 (22)	12 (8)
Insomnia $p < 0.001$[a]	13 (8)	28 (18)	8 (5)
Diarrhoea $p = 0.001$[a]	10 (6)	21 (13)	4 (3)
Pain: $p = 0.001$[a]	14 (9)	21 (13)	11 (7)
Headache	21 (13)	19 (12)	13 (8)
Dizziness	14 (9)	14 (9)	10 (7)
Muscle cramp	9 (6)	12 (8)	6 (4)
Fatigue	5 (3)	12 (8)	8 (5)
Accident	9 (6)	10 (6)	11 (7)
Agitation	7 (4)	10 (6)	11 (7)
Vomiting	5 (3)	10 (6)	7 (5)
Anorexia	6 (4)	10 (6)	4 (3)
Weight loss	3 (2)	8 (5)	3 (2)
Common cold	8 (5)	7 (4)	10 (7)
Abdominal disturbance	9 (6)	6 (4)	6 (4)
Urinary tract infection	10 (6)	6 (4)	20 (13) $p = 0.009$[b]
Stomach upset	8 (5)	5 (3)	1 (1)
Rhinitis	8 (5)	5 (3)	6 (4)
Upper respiratory tract infection	8 (5)	5 (3)	6 (4)
Oedema in extremities	1 (1)	4 (3)	8 (5)
Cough	2 (1)	3 (2)	8 (5)

[a] More frequent with donepezil (either dose).
[b] More frequent with placebo.

continued

TABLE 10 *Adverse events for donepezil (note that p-values are not reported unless stated) (cont'd)*

Rogers et *al.*, 1996[53] Adverse events: *n* (%)

Adverse event	**1. Donepezil 1 mg/day (*n* = 42)**	**2. Donepezil 3 mg/day (*n* = 40)**	**3. Donepezil 5 mg/day (*n* = 39)**	**Placebo (*n* = 40)**
Total no. of participants with ≥ 1 adverse event (%):	27 (64)	27 (64)	26 (67)	26 (65)
Gastrointestinal				
Nausea/vomiting	3 (7)	0	4 (10)	2 (5)
Diarrhoea	0	1 (3)	4 (10)	1 (3)
Gastric upset	0	2 (5)	3 (8)	2 (5)
Constipation	1 (2)	2 (5)	3 (8)	1 (3)
Other events				
Dizziness	2 (5)	1 (3)	3 (8)	4 (10)
Nasal congestion	1 (2)	5 (13)	2 (5)	3 (8)
Common cold	4 (10)	2 (5)	2 (5)	2 (5)
Headache	4 (10)	2 (5)	1 (3)	3 (8)
Flushing	4 (10)	1 (3)	1 (3)	1 (3)
Agitation	3 (7)	2 (5)	1 (3)	2 (5)
Urinary tract infection	1 (2)	3 (8)	1 (3)	2 (5)
Coughing	1 (2)	4 (10)	1 (3)	2 (5)
Accident	1 (2)	1 (3)	4 (10)	1 (3)
Pain	3 (7)	1 (3)	2 (5)	1 (3)

observed that rates were lower in the placebo groups, although this was not tested statistically. Ranges for 'serious' adverse events in the donepezil groups ranged from 7 to 24% and in the placebo groups ranged from 7 to 14%.

One unpublished trial reported rates of adverse events over 24 weeks in a population with mild AD.[55] These can be seen in *Table 12*. **[Confidential/academic confidential information removed]** Most adverse events were mild or moderate in nature; however, 5 and 7% identified in the donepezil-treated group were recorded as serious and severe, respectively. In the placebo group, the proportion rated serious was 3% and that rated severe was 2%.

TABLE 12 *Adverse event for* ***[Commercial/academic confidential information removed]***

All included studies report rates of participants withdrawing from the study because of adverse events. In general, withdrawals due to adverse events were in similar proportions between groups, although in three studies which included a group treated with 10 mg donepezil the rates withdrawing in these intervention groups were higher than in the placebo and the 5 mg donepezil groups within the same study.[50–52]

In one unpublished trial[55] whose participants had mild AD, the numbers withdrawing due to adverse events were **[Commercial/academic confidential information removed]**.

Withdrawals unrelated to adverse events show mixed data among included trials. Although some trials show no differences between treatment groups, some show more dropouts in the placebo groups and others show more in the treatment groups (which was often related to higher doses). No statistical comparisons were made in any of these studies. The numbers of deaths per treatment group were low in all studies, with no differences between groups noted. Data for withdrawals and deaths for each included trial are given in Appendix 7.

Summary

- Thirteen published and one unpublished RCTs of donepezil versus placebo over durations of 3–12 months met the inclusion criteria for the systematic review. The methodological quality and the quality of reporting in the studies were variable. Of the 13 published RCTs, six studies described an adequate randomisation schedule but only two of these appeared to limit fully the effects of selection bias by having adequate concealment of allocation.[49,54] Information to demonstrate a low likelihood of measurement bias was reported fully by only one study[54] and no studies appeared to guard against the effects of attrition bias. Eight RCTs reported that they were sponsored by the manufacturers.

TABLE 11 *Withdrawals due to adverse events for donepezil:* n *(%)*

AD2000 2004[43]				
	Donepezil 5–10 mg/day (*n* = 242)			**Placebo (*n* = 244)**
	36			20
Gauthier *et al.*, 2002[41]				
	Donepezil 10 mg/day (*n* = 102)			**Placebo (*n* = 107)**
	10%			5%
Greenberg *et al.*, 2000[54]				
	Donepezil 5 mg/day completers (*n* = 51)			**Placebo**
	0			Not reported
Homma *et al.*, 2000[44]				
	Donepezil 5 mg/day (*n* = 136)			**Placebo (*n* = 131) (1 excluded)**
	2 (1%)			6 (5%)
Krishnan *et al.*, 2003[45]				
	Donepezil 10 mg/day (*n* = 34)			**Placebo (*n* = 32)**
	0			1
Mohs *et al.*, 2001[46]				
	Donepezil 10 mg/day (*n* = 207)			**Placebo (*n* = 208)**
	23 (10.7), includes 3 that died			16 (7.4), includes 4 that died
Winblad *et al.*, 2001,[47] Wimo *et al.*, 2003[56]				
	Donepezil 10 mg/day			**Placebo**
	7%			6.3%
Burns *et al.*, 1999[50]				
	1. Donepezil 5 mg/day (*n* = 271)	**2. Donepezil 10 mg/day (*n* = 273)**		**3. Placebo (*n* = 274)**
Adverse events	24 (9)	50 (18)		27 (10)
Body as a whole	4 (1)	12 (4)		6 (2)
Cardiovascular	1 (<1)	5 (2)		3 (1)
Digestive	4 (1)	27 (10)		2 (<1)
Nervous	13 (5)	21 (10)		14 (5)
Rogers *et al.*, 1998[51]				
	1. Donepezil 5 mg/day (*n* = 154)	**2. Donepezil 10 mg/day (*n* = 157)**		**3. Placebo (*n* = 162)**
	6%	16%		7%
Rogers *et al.*, 1998[52]				
	1. Donepezil 5 mg/day (*n* = 157)	**2. Donepezil 10 mg/day (*n* = 158)**		**3. Placebo (*n* = 153)**
	7 (4)	14 (9)		2 (1)
Rogers *et al.*, 1996[53]				
	1. Donepezil 1 mg/day (*n* = 42)	**2. Donepezil 3 mg/day (*n* = 40)**	**3. Donepezil 5 mg/day (*n* = 39)**	**4. Placebo (*n* = 40)**
Adverse event(s)	5	2	3	2

- Because of the many differences between included trials, for example the use of different doses and varied patient populations, it was not possible to pool statistically all included trials.
- Six RCTs showed that donepezil appears to confer a statistically significant benefit to participants on the ADAS-cog scale when compared with placebo. The benefit varies according to the dose of donepezil, with higher doses of donepezil tending to show increasing benefit. Because the mean change scores varied considerably between the included studies, this dose-related trend can particularly be seen within individual trials, although no direct

statistical comparisons were made in any of these. The mean change scores were, however, varied between the included studies. Eight RCTs showed trends towards better MMSE score in the donepezil-treated groups when compared with the placebo groups, although this was not always demonstrated to be statistically significant. These trends were mirrored in one unpublished trial of people with mild AD.
- Seven RCTs assessed the effect of donepezil compared with placebo on the CGIC or CIBIC-plus, showing overall that CGIC/CIBIC-plus scores were statistically significantly better with donepezil. The range of scores varied between the included studies. Higher proportions of participants receiving donepezil were considered as responders to treatment, although this was not compared statistically in many cases. On the CDR scale trends were also demonstrated towards improved global function in the donepezil-treated groups compared with the placebo groups in five trials, but statistical significance was not demonstrated. In one unpublished trial with participants with mild AD, no benefit on the CDR was noted in the donepezil-treated group.
- A variety of functional measures were used in eight RCTs. Donepezil had some effect in improving or limiting further deterioration on ADLs when compared with placebo, but this was not always statistically significant, particularly over longer durations of follow-up. One trial reported time to loss of ADL and/or time to institutional care and found that donepezil conferred no advantage over placebo.
- The NPI was used as a measure of mood and behaviour in four RCTs. Data were varied but suggested that donepezil may have some effect in improving or limiting further deterioration on the NPI scale compared with placebo, at least over shorter durations of follow-up.
- Patient QoL was assessed in three studies; no measures used were validated QoL scales for these populations. There is no clear pattern from these studies with reports of improvements, no change and worsening; the impact of dose on QoL is also unclear. Similarly, the data on effects on carer burden and mental well-being are limited.
- Adverse events affect participants receiving donepezil more than those on placebo, and higher doses of donepezil increased the incidence of people suffering from adverse events. Nausea, vomiting and diarrhoea were the main adverse events. Most were described as mild to moderate. Withdrawals due to adverse events generally resulted in similar losses between the low-dose donepezil groups and placebo; however, higher doses of donepezil tended to lead to more withdrawals.
- Studies were generally of a short duration and it is difficult to judge the long-term consequences. In the two trials of 1-year duration the effects of donepezil did appear to remain favourable to donepezil; however, in a third the effects appeared to be less conclusive, taking all outcomes into account. In addition, it is difficult to assess the meaning of the changes on these outcomes for people with AD and their carers.

Rivastigmine

Quantity and quality of research available

Four published RCTs and two unpublished RCTs met the inclusion criteria for the review, and the details of these are shown in *Table 13*. **[Commercial/academic confidential information removed]** Participants included in all trials were classified as having probable AD of mild to moderate severity.

The published trials all had three treatment arms, comparing various dosage levels of rivastigmine with placebo. Two trials[57,58] had treatment groups with doses of 1–4 and 6–12 mg/day (flexible-dose studies) and one trial had doses of 4 and 6 mg/day.[59] By the end of follow-up, the mean doses were similar for the two flexible-dose studies: 3.7 and 10.4 mg/day for the two groups in one[58] and 3.5 and 9.7 mg/day for the two groups in another.[57] The remaining trial[60] compared the effects of a twice-daily regimen compared with a three-times daily regimen, giving average doses of 9.6 and 10.1 mg/day, respectively. The published trials were all multicentre studies, with total sample sizes ranging from 114 to 725 participants. Treatment duration ranged from 13 to 26 weeks.

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The quality of reporting and methodology of the included published studies varied (*Table 14*). Only two studies reported an adequate method of randomisation. One study[60] did not report their method of randomisation and another[59] reported randomisation in an inadequate way. Concealment of allocation was not clear in any of the trials except in one study.[57] Selection bias may therefore affect interpretation of some of these trials' results. Participants and care providers were adequately blinded in two of the studies,[58,59] with treatment

TABLE 13 *Characteristics of included published studies for rivastigmine*

Study	Methods	Participants	Outcomes
Agid *et al*., 1998[59]	*Design*: multicentre RCT *Interventions*: 1. Rivastigmine 4 mg/day; 2. Rivastigmine 6 mg/day; 3. Placebo *Number of centres*: 54 *Duration of treatment*: titration followed by 10 weeks of treatment, a total of 13 weeks *Sponsor*: Novartis Pharmaceutical	*Inclusion criteria*: mild-to-moderate dementia (DSM III), and probable AD (NINCDS-ADRDA) *Numbers*: 402 randomised 1. 136 to 4 mg/day 2. 133 to 6 mg/day 3. 133 to placebo *Mean ages (±SD)*: 1. 68.62 ± 8.64 years 2. 68.68 ± 7.85 years 3. 70.80 ± 8.58 years	• CGIC • Fuld Object Memory Evaluation (FOME) • Digit Symbol Substitution Test (DSST) • Benton Visual Retention Test (BVRT) • Trail making test (TMT) • MMSE • NOSGER • ADL • Adverse events
Corey-Bloom *et al*., 1998[57]	*Design*: multicentre RCT *Interventions*: 1. Rivastigmine 1–4 mg/day 2. Rivastigmine 6–12 mg/day 3. Placebo *Number of centres*: 22 *Duration of treatment*: 26 weeks, including 7 weeks dose titration *Sponsor*: Novartis Pharmaceutical	*Inclusion criteria*: 45–89 years; probable AD by DSM-IV and NINCDS-ADRDA criteria; MMSE 10–26 *Numbers*: 699 randomised 1. 233 to 1–4 mg/day 2. 231 to 6–12 mg/day 3. 235 to placebo *Mean age (range)*: 1. 74.9 (45–89) 2. 73.8 (50–89) 3. 74.8 (45–89) (p = ns)	*Primary outcomes*: • ADAS-cog • CIBIC-plus • ADL • PDS *Secondary outcomes*: • MMSE • GDS • Adverse events
Forette *et al*., 1999[60]	*Design*: multicentre RCT *Interventions*: 1. Rivastigmine 2× a day, mean dose 9.6 mg/day 2. Rivastigmine 3× a day, mean dose 10.1 mg/day 3. Placebo *Number of centres*: 11 *Duration of treatment*: 18 weeks, including 10 week dose titration *Sponsor*: Novartis Pharmaceutical	*Inclusion criteria*: mild to moderate dementia (DSM-III-R), probable AD (NINCDS-ADRDA); MMSE 12–26 *Numbers*: 114 randomised 1. 45 to 2× a day 2. 45 to 2× a day 3. 24 to placebo *Mean age*: 1. 69.5 ± 9.9 2. 71.7 ± 6.8 3. 72.5 ± 4.8	*Primary outcomes*: • ADAS-cog • Weschler logical memory test • Digit span test • Word fluency • CIBIC-plus • NOSGER *Secondary outcomes*: • Adverse events • Compliance • Overall tolerability
Rösler *et al*., 1999[58]	*Design*: multicentre RCT *Interventions*: 1. Rivastigmine 1–4 mg/day 2. Rivastigmine 6–12 mg/day 3. Placebo *Number of centres*: 45 *Duration of treatment*: 26 weeks, including 12 weeks dose escalation *Sponsor*: Novartis Pharmaceutical	*Inclusion criteria*: aged 50–85 years; AD (DSM-IV), probable AD (NINCD-ADRDA), MMSE 10–26 *Numbers*: 725 randomised 1. 243 to 1–4 mg/day 2. 243 to 6–12 mg/day, 3. 239 to placebo *Mean age*: 72 (range 45–95)	*Primary outcomes*: • ADAS-cog • CIBIC-plus • PDS *Secondary outcomes*: • MMSE • GDS • Adverse events
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TABLE 14 *Quality assessment for rivastigmine*

Study	Randomisation	Concealment of allocation	Baseline characteristics	Eligibility criteria	Blinding of assessors	Care provider Blinding	Blinding of patient	Primary outcome results	ITT analysis	Withdrawals explained
Agid *et al*., 1998[59]	In	Un	Rep	Par	Un	Ad	Ad	Ad	In	In
Corey-Bloom *et al*., 1998[57]	Ad	Ad	Rep	Ad	Un	Par	Par	Ad	Ad	Ad
Forette *et al*., 1999[60]	Un	Un	Un	Ad	Par	Un	Un	Ad	In	Par
Rösler *et al*., 1999[58]	Ad	Ad	Un	Ad	Un	Ad	Ad	Ad	Ad	Ad
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Ad, adequate; In, inadequate; Par, partial; Rep, reported; Un, unknown.

and placebo medication having the same physical appearance and number of capsules for each dose. Reporting was unclear[60] or partial[57] for the other two studies. None of the studies reported assessor blinding clearly. Measurement bias may have affected the results of some of these trials.

Baseline characteristics were only reported clearly by one study.[57] One study[60] only presented baseline characteristics for participants completing the study, another[59] only reported baseline ages for the three groups. All but one of the RCTs reported adequate eligibility criteria, with the remaining study[59] reporting a required diagnosis of mild-to-moderate dementia (DSM-III) and probable AD on the NINCDS-ADRDA criteria, but not specifying an MMSE range.

Point estimates and measures of variability for primary outcomes were presented adequately in all studies. ITT analysis was presented in two of the studies[57,58] and both of these studies also described withdrawals adequately. One study[60] conducted an ITT analysis on safety measures, but an observed case analysis on efficacy measures. Reasons for patient withdrawal were only partially reported by this study. ITT was not used by the remaining study[59] and withdrawals were inadequately explained in the report.

The studies by Corey-Bloom and colleagues[57] and Rösler and colleagues[58] both calculated that ~200 people were required in each group to enable 90% power with $\alpha = 0.05$ for detecting at least a 3-point improvement on the ADAS-cog scale and an increase from 15–30% in participants classified as responders on the CIBIC scale (i.e. with scores of <4). Power calculations were not reported in the other two studies.[59,60]

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Assessment of effectiveness

Cognitive measures

ADAS-cog

Three of the four included published studies reported the ADAS-cog, and the results are shown in *Table 15* (negative scores indicate deterioration). At baseline, all three studies had similar mean ADAS-cog scores for all treatment groups (ranging from 21.7 to 24.0) and there were no statistically significant differences between treatment groups for any of the studies. The baseline scores of participants in the study by Rösler and colleagues[58] show a broad range, with the 1–4 mg/day rivastigmine dose group ranging from 4.0 to 60.7 and the placebo group ranging from 3.3 to 57.8. Forette and colleagues[60] presented SDs which suggest a degree of variation among participants at baseline: 24.0 ± 11.6 for the twice daily group, 23.2 ± 8.5 for the three times daily group and 21.7 ± 8.8 for the placebo group. However, this study had very low sample sizes and no statistically significant differences were reported between the treatment groups and placebo at baseline.

The study comparing twice with three times daily[60] found no statistically significant difference between the treatment groups and placebo in terms of changes in ADAS-cog score from baseline. The two other studies which reported this outcome measure both found a statistically significant difference between the high-dose group

TABLE 15 *ADAS-cog for rivastigmine*

Corey-Bloom *et al.*, 1998[57] Mean change from baseline (95% CI)			
1. Rivastigmine 1–4 mg (*n* = 233)	**2. Rivastigmine 6–12 mg (*n* = 231)**	**3. Placebo (*n* = 234)**	***p*-Value versus placebo**
2.36 (3.13 to 1.59)	0.31 (1.08 to –0.46)	4.09 (4.86 to 3.32)	2. $p < 0.001$
Forette *et al.*, 1999[60] Mean change from baseline *Numbers estimated from figure*			
1. Rivastigmine b.d. (*n* = 23)	**2. Rivastigmine t.d.s (*n* = 28)**	**3. Placebo (*n* = 19)**	***p*-Value versus placebo**
–2.6	*0.4*	*2.0*	No significant differences
Rösler *et al.*, 1999[58] Mean change from baseline (95% CI)			
1. Rivastigmine 1–4 mg/day (*n* = 243)	**2. Rivastigmine 6–12 mg/day (*n* = 243)**	**3. Placebo (*n* = 239)**	***p*-Value versus placebo**
1.37 (2.27 to 0.53)	–0.26 (0.66 to –1.06)	1.34 (2.19 to 0.41)	2. $p = 0.011$
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(6–12 mg/day) and placebo, but not between the low-dose group (1–4 mg/day) and placebo.

In the study by Corey-Bloom and colleagues,[57] participants in the high-dose group showed an average decline that was 3.78 points less than the decline shown by placebo participants. It should be noted that data in this study were presented incorrectly in the published paper. The table of results showed negative changes of –2.36 for the low-dose group, –0.31 for the high-dose group and –4.09 for the placebo group, suggesting that placebo participants had improved more than treatment participants (since a negative mean change on ADAS-cog indicates clinical improvement). However, the discussion in the paper indicated that the treatment participants had improved statistically significantly compared with placebo participants, and a graph showing the observed case analysis showed the signs reversed, so it is assumed that the authors made an error in the first table, and that the results should have read 2.36 for the low-dose group, 0.31 for the high-dose group and 4.09 for the placebo group.

The study by Rösler and colleagues[58] also contained this error in reporting. The signs have been reversed in *Table 15* to reflect the fact that a negative change indicates improvement, not a positive one. The authors found a difference of 1.6 points between endpoint mean scores for the high-dose treatment group and placebo. All participants in the study by Corey-Bloom and colleagues[57] showed a greater deterioration compared with those in the study by Rösler and colleagues.[58] The average age of participants in the latter study[58] was 74.9 years for low-dose participants and 74.8 years for placebo participants, compared with a mean age of 72 years for all participants in the other study.[57]

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Rösler and colleagues[58] also presented data on 'cognitive responders', who are defined as those with at least a 4-point improvement on the ADAS-cog scale; 24% of the high-dose group (6–12 mg/day) were considered to be cognitive responders, compared with 15% of the low-dose group (1–4 mg/day) and 16% of the placebo group. Comparison between the high-dose group and placebo showed no statistically significant difference ($p < 0.1$).

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Two of the four published studies (Corey-Bloom and colleagues[57] and Rösler and colleagues[58]) provided data (mean change and 95% CI) that allowed them to be combined in a meta-analysis (*Figure 11*). Pooling the data using either a random-effects model or a fixed-effect model showed statistically significant heterogeneity (χ^2 test for heterogeneity 5.24, df = 1, $p = 0.022$). Statistically significant heterogeneity was also

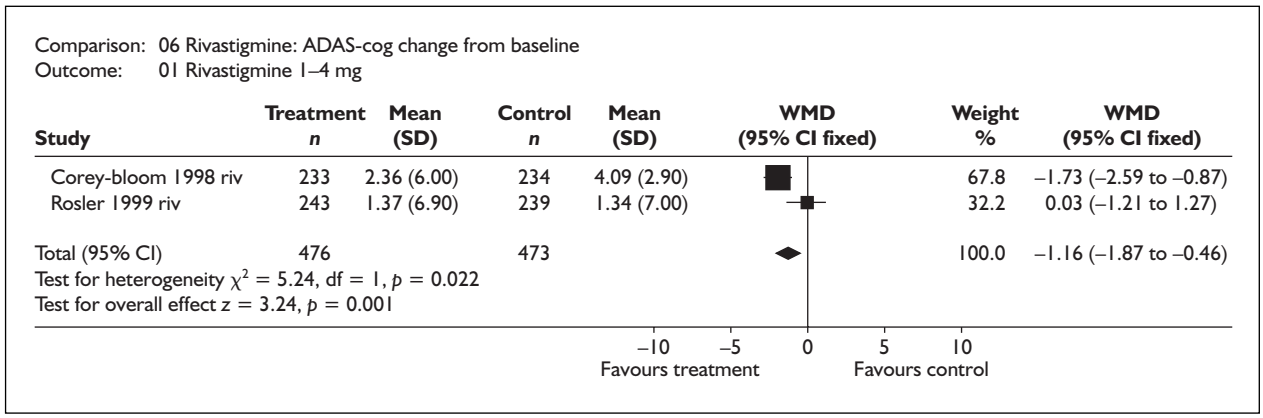

FIGURE 11 *ADAS-cog change from baseline with rivastigmine 1–4 mg*

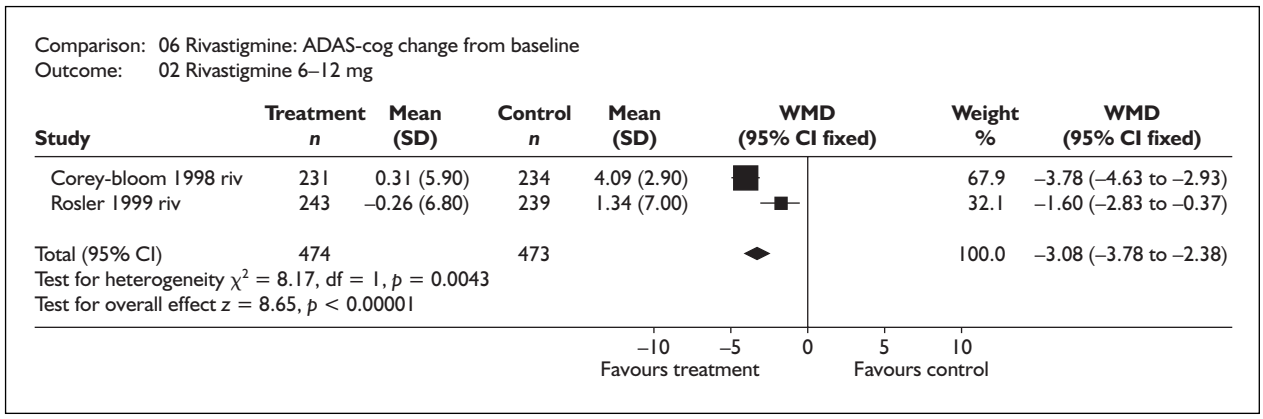

FIGURE 12 *ADAS-cog change from baseline with rivastigmine 6–12 mg*

found when combining the studies for the 6–12 mg/day dose group (χ^2 test 8.17, df = 1, $p = 0.0043$), so the statistically significant treatment effect seen for the fixed-effect model combining the two trials with this dosage group is not valid (WMD –3.08, 95% CI –3.78 to –2.38, $p < 0.00001$) (see *Figure 12*). Exploration of this statistical heterogeneity by subgroup analysis was not appropriate owing to the small numbers of included trials in the meta-analysis.

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MMSE

Three of the four published studies reported MMSE as an outcome measure (*Table 16*). Two of these reported mean baseline scores of 19–20,[57,58] but baseline values were not reported in the other study. The first study compared two fixed-dose groups (4 and 6 mg/day) with placebo, and the other two studies compared two flexible dose groups (1–4 and 6–12 mg/day) with placebo. The fixed-dose study did not report any statistically significant differences between treatment groups and placebo for this outcome measure. Both of the flexible dose studies reported a statistically significant difference between the high dose treatment group and placebo. The high-dose participants in both studies had a mean dose of ~10 mg/day. Corey-Bloom and colleagues[57] used observed case analysis for this outcome measure, and found an improvement in the high-dose group of 0.30 points, compared with a decline in placebo participants of –0.79 points. The other flexible dose study[58] used ITT analysis, and reported an improvement in the high-dose group of 0.21 points compared with a decline in placebo participants' scores of –0.47. In this study, the low-dose participants also showed a decline in MMSE score, with a mean change of –0.62, but this was not statistically significantly different from the placebo group.

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TABLE 16 *MMSE for rivastigmine*

Agid *et al.*, 1998[59] Mean change from baseline			
1. Rivastigmine 4 mg/day (*n* = 111)	**2. Rivastigmine 6 mg/day (*n* = 103)**	**3. Placebo (*n* = 117)**	***p*-Value versus placebo**
0.0 ± 3.3	0.3 ± 3.1	–0.0 ± 2.6	Not reported
Corey-Bloom *et al.*, 1998[57] *Observed case analysis*			
1. Rivastigmine 1–4 mg/day (*n* = 233)	**2. Rivastigmine 6–12 mg/day (*n* = 231)**	**3. Placebo (*n* = 234)**	***p*-Value versus placebo**
–0.34	0.30	–0.79	2. $p < 0.05$
Rösler *et al.*, 1999[58] Mean change from baseline (95% CI)			
1. Rivastigmine 1–4 mg/day (*n* = 243)	**2. Rivastigmine 6–12 mg/day (*n* = 243)**	**3. Placebo (*n* = 239)**	***p*-Value versus placebo**
–0.62 (–1.05 to –0.15)	0.21 (–0.24 to 0.64)	–0.47 (–0.96 to –0.04)	2. $p < 0.05$
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BVRT

The Benton Visual Retention Test (BVRT) was used as an outcome measure by Agid and colleagues.[59] The low-dose (4 mg/day) group's mean change in score was 0.3 (SD 2.6), the high-dose group changed by 0.2 (SD 2.6) points on average and the placebo group's mean change was 0.2 (SD 2.7). No statistically significant differences were reported.

TMT

Agid and colleagues[59] reported on the Trail Making Test (TMT), which assesses speed of visual search, attention, mental flexibility and motor function. The score is the time taken to complete a test successfully. The study compared two treatment dose groups (4 and 6 mg/day) with placebo. The mean changes from baseline score were –1.6 ± 39.0, –7.3 ± 48.9 and 0.5 ± 28.7 for the low-dose, high-dose and placebo groups, respectively. No statistically significant differences were observed between the two treatment groups and the placebo group.

Wechsler logical memory test

Forette and colleagues[60] reported on the immediate recall aspect of the Wechsler Logical Memory Test. This test is part of the Wechsler Memory Scale, which is the most frequently used clinical measure of memory in the USA. They found that participants receiving twice daily doses of rivastigmine scored better than those participants receiving treatment medication three times daily. Mean scores for these two groups were 1.8 ± 2.3 and 0.1 ± 2.3, respectively, $p = 0.012$.

FOME

Agid and colleagues[59] used the Fuld Object Memory Evaluation (FOME) as an outcome measure. They reported two aspects of the evaluation: 'total storage' and 'total retrieval'. At week 13, total storage was statistically significantly better for both the high-dose group (6 mg/day) and the low-dose group (4 mg/day) than for placebo (0.7 ± 6.2 and 0.4 ± 6.2 versus –0.9 ± 5.5, respectively, $p \leq 0.05$). For the retrieval part of the test, only the high-dose group was statistically significantly better than placebo at 13 weeks (1.1 ± 4.2 versus 0.1 ± 4.3, $p \leq 0.05$).

DSST

Agid and colleagues[59] used the Digit Symbol Substitution Subtest (DSST) as an outcome measure. The DSST is a subset of the WAIS-R. At week 13, there was a statistically significant difference of 2.3 between the high-dose group (6 mg/day) and placebo (2.8 ± 8.1 versus 0.5 ± 6.9, $p < 0.05$). The difference between the low-dose group (4 mg/day) and placebo group was 1.2, but this was not statistically significant. Forette and colleagues list the digit span subset of the WAIS-R as an outcome measure, but do not present results as there was no statistically significant difference found between treatment and placebo groups for this test.

Summary: statistically significant differences between the 6–12 mg/day treatment groups (mean dose ~10 mg/day) and placebo were reported by two trials for both ADAS-cog and MMSE. **[Commercial/academic confidential information removed]**

Global measures

CIBIC-plus. Three of the four included published studies used CIBIC-plus as an outcome measure, and changes from baseline can be seen for two of these studies in *Table 17*. Despite having similar sample sizes and treatment groups with similar mean doses, the two studies showed different changes from baseline. Both studies found a statistically significant difference between the high-dose treatment group (6–12 mg/day) and placebo but not between the low-dose groups and placebo. Corey-Bloom and colleagues[57] reported an average difference of 0.29 points between high-dose and placebo participants, and Rösler and colleagues[58] reported a difference of 0.53 points.

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Two of the studies calculated the percentage of improvers or responders on this scale, i.e. participants gaining CIBIC-plus scores of one, two or three, and these are shown in *Table 18*. Rösler and colleagues[58] reported a statistically significant difference between both the low- and high-dose treatment groups compared with placebo. Another study[60] found that 57% of participants receiving rivastigmine twice daily were classified as responders compared with 16% of placebo participants, and this difference was statistically significant. Some 36% of participants who received rivastigmine three times a day were classified as responders, but this was not statistically significantly different to the placebo group's percentage of responders.

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TABLE 17 *CIBIC-plus for rivastigmine*

Corey-Bloom et *al*., 1998[57] Mean change from baseline (95% CI)			
1. Rivastigmine 1–4 mg/day (*n* = 233)	**2. Rivastigmine 6–12 mg/day (*n* = 231)**	**3. Placebo (*n* = 234)**	***p*-Value versus placebo**
0.23 (0.07 to 0.39)	0.20 (0.04 to 0.36)	0.49 (0.33 to 0.65)	2. $p < 0.01$
Rösler et *al*., 1999[58] Mean change from baseline (95% CI)			
1. Rivastigmine 1–4 mg/day (*n* = 243)	**2. Rivastigmine 6–12 mg/day (*n* = 243)**	**3. Placebo (*n* = 239)**	***p*-Value versus placebo**
4.24 (4.02 to 4.38)	3.91 (3.71 to 4.09)	4.38 (4.22 to 4.58)	2. $p < 0.001$
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TABLE 18 *CIBIC-plus responders for rivastigmine*

Forette et *al*., 1999[60] Percentage of responders			
1. Rivastigmine b.d. (*n* = 23)	**2. Rivastigmine t.d.s. (*n* = 28)**	**3. Placebo (*n* = 19)**	***p*-Value versus placebo**
57	36	16	1. $p = 0.027$
Rösler et *al*., 1999[58] Number (%) of responders			
1. Rivastigmine 1–4 mg/day (*n* = 243)	**2. Rivastigmine 6–12 mg/day (*n* = 243)**	**3. Placebo (*n* = 239)**	***p*-Value versus placebo**
69/233 (30)	80/219 (37)	46/230 (20)	1. $p < 0.05$ 2. $p < 0.001$
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GDS. The GDS was used as an outcome measure by two of the four published studies included in this review (*Table 19*). Both studies compared high- and low-dose treatment groups with a placebo group, and found that the high-dose group (6–12 mg/day) participants showed statistically significantly less deterioration than placebo participants. On average, the high-dose groups' scores deteriorated by ~0.2 points less than the placebo groups' scores.

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CGIC. Agid and colleagues[59] reported the percentage of participants with a 'successful' CGIC assessment, i.e. scoring 1 or 2 on the scale. The study compared both a low-dose group (4 mg/day) and a high-dose group (6 mg/day) with a placebo group. A statistically significantly higher percentage of high-dose participants scored 1 or 2 compared with placebo participants (42.72% versus 29.91%, $p = 0.05$); 31.53% of the low-dose group were classified as successful, but this was not statistically significantly better than the success rate in the placebo group.

Summary: high-dose participants generally performed better than placebo participants on global outcome measures, with statistically significant improvements reported for CIBIC-plus, CGIC assessment and the GDS measure.

Functional measures

PDS

Two published studies reported outcomes on the PDS (*Table 20*), where a change towards a positive score indicates clinical improvement.

Both studies compared two flexible dose groups against a placebo group. Corey-Bloom and colleagues[57] reported a statistically significant

TABLE 19 *GDS for rivastigmine*

Corey-Bloom et *al*., 1998[57] GDS (95% CI)			
1. Rivastigmine 1–4 mg/day (*n* = 233)	**2. Rivastigmine 6–12 mg/day (*n* = 231)**	**3. Placebo (*n* = 234)**	***p*-Value versus placebo**
–0.16 (–0.25 to –0.07)	–0.13 (–0.22 to –0.04)	–0.32 (–0.41 to –0.23)	2. $p < 0.03$
Rösler et *al*., 1999[58] GDS (95% CI)			
1. Rivastigmine 1–4 mg/day (*n* = 243)	**2. Rivastigmine 6–12 mg/day (*n* = 243)**	**3. Placebo (*n* = 239)**	***p*-Value versus placebo**
–0.22 (–0.3 to –0.1)	–0.06 (–0.2 to 0.0)	–0.26 (–0.4 to –0.2)	2. $p < 0.05$
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TABLE 20 *PDS for rivastigmine*

Corey-Bloom et *al*., 1998[57] PDS (95% CI)			
1. Rivastigmine 1–4 mg/day (*n* = 233)	**2. Rivastigmine 6–12 mg/day (*n* = 231)**	**3. Placebo (*n* = 234)**	***p*-Value versus placebo**
–5.19 (–6.52 to –3.86)	–1.52 (–2.85 to –0.19)	–4.90 (–6.22 to –3.58)	2. $p < 0.001$
Rösler et *al*., 1999[58] PDS (95% CI)			
1. Rivastigmine 1–4 mg/day (*n* = 243)	**2. Rivastigmine 6–12 mg/day (*n* = 243)**	**3. Placebo (239)**	***p*-Value versus placebo**
–3.37 (–4.99 to –1.61)	0.05 (–1.57 to 1.77)	–2.18 (–3.91 to –0.49)	2. $p = 0.07$
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difference of 3.38 points between the 6–12 mg/day rivastigmine participants and the placebo group, but Rösler and colleagues[58] did not find a statistically significant difference. The low-dose group in the study by Corey-Bloom and colleagues[57] showed a lower score change than placebo participants, with a mean change of –5.19, but this was not statistically significant. High-dose participants in the study by Rösler and colleagues showed a clinical improvement, with an average improvement of 0.05 compared with the mean change of –2.18 in the placebo group. Again, changes were smaller in the low-dose group, with a mean of –3.37.

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The study by Rösler and colleagues[58] also reported the number and percentage of participants in each group who showed an improvement of at least 10%. A statistically significantly higher proportion of participants in the high-dose group compared with those in the placebo group demonstrated this level of improvement (29 versus 19%). In the low-dose group, 19% of participants showed an improvement of at least 10%.

Summary: participants treated with 6–12 mg/day rivastigmine demonstrated statistically significantly better functional outcomes than placebo participants, based on the PDS measure discussed here.

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Behaviour and mood measures

NOSGER

Two published studies reported the Nurses Observation Scale for Geriatric Participants (NOSGER). Changes from baseline are shown in *Table 21*. Agid and colleagues[59] compared two different dose treatment groups with placebo. No *p*-values were reported for this outcome measure, but the high-dose rivastigmine group (6–12 mg/day) seemed to show an average improvement in memory and IADL performance (mean differences of –0.2 and –0.5, respectively). Forette and colleagues[60] compared twice daily/three-times daily doses of rivastigmine with placebo. This study reported a statistically significant improvement in memory assessment for both treatment groups compared with placebo (mean difference between high-dose group and placebo was 2.3, mean difference between low-dose group and placebo was 2.0). No statistically significant differences were reported for other components of the NOSGER assessment, i.e. those assessing mood and behaviour.

Summary: on measures of behaviour and mood no statistically significant benefit was demonstrated in the rivastigmine-treated groups compared to the placebo groups.

TABLE 21 *NOSGER for rivastigmine*

Agid *et al.*, 1998[59]			
1. Rivastigmine 4 mg/day (*n* = 111)	**2. Rivastigmine 6 mg/day (*n* = 103)**	**3. Placebo (*n* = 117)**	***p*-Value versus placebo**
Memory: 0.7 ± 2.8	Memory: –0.2 ± 2.4	Memory: 0.0 ± 3.4	Not reported
IADL: 0.0 ± 3.3	IADL: –0.7 ± 3.5	IADL: –0.2 ± 3.3	Not reported
Self-care: 0.2 ± 2.8	Self-care: –0.1 ± 2.1	Self-care: 0.1 ± 2.7	Not reported
Mood: 0.2 ± 2.8	Mood: 0.1 ± 2.5	Mood: 0.1 ± 3.1	Not reported
Social behaviour: –0.3 ± 3.1	Social behaviour: –0.5 ± 3.0	Social behaviour: 0.0 ± 3.6	Not reported
Disturbing behaviour: 0.2 ± 2.2	Disturbing behaviour: –0.5 ± 2.3	Disturbing behaviour: –0.0 ± 2.1	Not reported
Forette *et al.*, 1999[60]			
1. Rivastigmine b.d. (*n* = 23)	**2. Rivastigmine t.d.s. (*n* = 27)**	**3. Placebo (*n* = 19)**	***p*-Value versus placebo**
Memory: –0.7 ± 2.9	Memory: –1.0 ± 2.7	Memory: 1.3 ± 3.7	1. $p = 0.037$ 2. $p = 0.014$
IADL: 0.4 ± 3.1	IADL: –0.7 ± 4.0	IADL: 0.8 ± 4.0	Not reported
Self-care: –0.4 ± 2.0	Self-care: –0.6 ± 2.4	Self-care: –0.3 ± 2.5	Not reported
Mood: 0.7 ± 3.0	Mood: –0.4 ± 3.4	Mood: –0.6 ± 3.2	Not reported
Social behaviour: 0.0 ± 2.6	Social behaviour: –1.1 ± 3.8	Social behaviour: 0.3 ± 3.3	Not reported
Disturbing behaviour: –0.3 ± 2.1	Disturbing behaviour: –0.7 ± 3.4	Disturbing behaviour: 0.1 ± 3.1	Not reported

Compliance

Rösler and colleagues[58] reported that two of the 34 withdrawals in the low-dose group (n = 243) withdrew owing to non-compliance; likewise, three of 79 withdrawals in the high-dose group (n = 243) and one of 31 withdrawals in the placebo group (n = 239) were due to non-compliance. Forette and colleagues[60] listed compliance as a secondary outcome (counting capsules) but did not present data on this. One placebo patient withdrew owing to non-compliance in the study by Corey-Bloom and colleagues,[57] but none of the treatment participants did. The study by Agid and colleagues[59] did not mention compliance.

[Commercial/academic confidential information removed]

Adverse events

Adverse events reported in the four included published trials **[Commercial/academic confidential information removed]** can be seen in *Table 22*.

Four included published studies reported adverse events for rivastigmine, but only two of the studies reported p-values for statistically significant results. Most reported adverse events related to the gastrointestinal system, dizziness and headaches. **[Commercial/academic confidential information removed]**

Nausea and vomiting

Nausea was reported much more frequently by participants treated with rivastigmine compared with placebo participants, with rates of 8–58% for rivastigmine participants and 3–11% for placebo groups. Agid and colleagues[59] found that 25% more high-dose participants than placebo participants reported nausea. Corey-Bloom and colleagues[57] reported higher nausea rates for the high-dose group compared with placebo; 37% higher during the titration phase and 50% higher during the maintenance phase. Statistically significant differences between treatment and placebo groups were reported in both studies with 1–4 mg/day and 6–12 mg/day groups.[57,58] Rates of reporting for vomiting were 2–10% for placebo participants and 8–38% for rivastigmine participants. Both of the studies presenting p-values reported statistically significant differences between vomiting incidence in the

TABLE 22 *Adverse events for rivastigmine (note that* p*-values are not reported unless stated)*

Agid et *al.*, 1998[59] *n* (%)			
Adverse event	**Rivastigmine 4 mg/day (*n* = 136)**	**Rivastigmine 6 mg/day (*n* = 133)**	**Placebo (*n* = 133)**
Nausea	23 (17)	41 (31)	8 (6)
Vomiting	13 (10)	24 (18)	4 (3)
Diarrhoea	9 (7)	16 (12)	2 (2)
Abdominal pain	8 (6)	9 (7)	7 (5)
Dizziness	8 (6)	26 (20)	9 (7)
Headache	6 (4)	17 (13)	8 (6)
Corey-Bloom et *al.*, 1998[57] Titration phase (%)			
Adverse event	**Rivastigmine 1–4 mg/day**	**Rivastigmine 6–12 mg/day**	**Placebo**
Sweating	2	6*	2
Fatigue	5	10*	4
Asthenia	2	10*	2
Weight decrease	1	4*	1
Malaise	1	3*	1
Allergy	2*	0	0
Hypertension	4*	3	1
Dizziness	15	24*	13
Somnolence	7	9*	2
Nausea	14	48*	11
Vomiting	7	27*	3
Anorexia	8*	20*	3
Flatulence	2	5*	1

* $p < 0.05$ from placebo.

continued

TABLE 22 *Adverse events for rivastigmine (note that p-values are not reported unless stated) (cont'd)*

Corey-Bloom *et al.*, 1998[57] Maintenance phase (%)

Adverse event	Rivastigmine 1–4 mg/day	Rivastigmine 6–12 mg/day	Placebo
Dizziness	8	14*	4
Nausea	8*	20*	3
Vomiting	5*	16*	2
Dyspepsia	6*	5*	1
Sinusitis	1	4*	1

* $p < 0.05$ from placebo.

Forette *et al.*, 1999[60] Incidence (%)

Adverse event	Rivastigmine b.d. ($n = 45$)	Rivastigmine t.d.s. ($n = 45$)	Placebo ($n = 24$)
Nausea	58	58	8
Vomiting	38	31	4
Dizziness	27	9	0
Anorexia	18	16	0
Headache	16	20	4

Rösler *et al.*, 1999[58] No. (%) of adverse events occurring at 5% more often with rivastigmine than in placebo or occurring with an incidence significantly different from placebo

Adverse event	Rivastigmine 1–4 mg/day ($n = 242$) (1 missing)	Rivastigmine 6–12 mg/day ($n = 242$) (1 missing)	Placebo ($n = 239$)
Nausea	41 (17)*	121 (50)*	23 (10)
Vomiting	19 (8)	82 (34)*	14 (6)
Dizziness	25 (10)	48 (20)*	17 (7)
Headache	16 (7)	45 (19)*	18 (8)
Diarrhoea	23 (10)	40 (17)*	21 (9)
Anorexia	8 (3)	34 (14)*	4 (2)
Abdominal pain	11 (5)	29 (12)*	7 (3)
Fatigue	5 (2)	23 (10)*	6 (3)
Malaise	3 (1)	23 (10)*	5 (2)

* $p < 0.05$ from placebo.

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[Commercial/academic confidential information removed]

high-dose (6–12 mg/day) groups and the placebo groups: Corey-Bloom and colleagues[57] reported 27% compared with 3% during the dose titration phase and 16% compared with 2% during the dose maintenance phase; Rösler and colleagues[58] reported vomiting rates of 28% among the high-dose group and 6% for placebo participants.

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Diarrhoea

Diarrhoea incidence was reported in only two of the four published studies. Rösler and colleagues[58] reported a statistically significant difference between the high-dose group (6–12 mg/day) and placebo (17 versus 9%). Agid and colleagues[59] did not present *p*-values, but reported incidence rates of 7, 12 and 2 for the low-dose (4 mg/day), high-dose (6 mg/day) and placebo groups, respectively.

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Dizziness

All four published studies reported the incidence of dizziness, which ranged from 0 to 13% in placebo participants and from 6 to 27% in treatment participants. The two studies which presented *p*-values both reported statistically significant differences between placebo participants and participants in high-dose groups (6–12 mg/day), with rates of 24 versus 13% being reported by Corey-Bloom and colleagues[57] and 20 versus 7% by Rösler and colleagues.[58] However, the incidence rates for the low-dose groups in

TABLE 23 *Withdrawals due to adverse events for rivastigmine*

Agid *et al.*, 1998[59] Incidence (%)			
	Rivastigmine 4 mg/day (*n* = 136)	**Rivastigmine 6 mg/day (*n* = 133)**	**Placebo (*n* = 133)**
	14 (10)	16 (12)	5 (4)
Corey-Bloom *et al.*, 1998[57] Incidence (%)			
	Rivastigmine 1–4 mg/day	**Rivastigmine 6–12 mg/day**	**Placebo**
	19 (8.2)	66 (28.6)	17 (7.2)
Forette *et al.*, 1999[60] Incidence (%)			
	Rivastigmine b.d. (*n* = 45)	**Rivastigmine t.d.s. (*n* = 45)**	**Placebo (*n* = 24)**
	9 (20)	5 (11.1)	1 (4.2)
Rösler *et al.*, 1999[58] Incidence (%)			
	Rivastigmine 1–4 mg/day (*n* = 242)	**Rivastigmine 6–12 mg/day (*n* = 242)**	**Placebo (*n* = 239)**
	18 (7)	55 (23)	16 (7)
[Commercial/academic confidential information removed]			
[Commercial/academic confidential information removed]			

these studies were not statistically significantly higher than for placebo groups. One of the studies which did not present *p*-values reported incidents rates of 6, 20 and 7% for 4 and 6 mg/day and placebo groups, respectively,[59] and the other reported rates of 27 for the twice daily group, 9% for the three times daily group and 0% for the placebo group (although this study had very low sample sizes).[60]

[Commercial/academic confidential information removed]

Headache

Three of the included published studies reported incidence rates for headache, and all but one of these reported a higher rate for treatment groups than for placebo groups. Only Rösler and colleagues[58] reported *p*-values, and these showed that the 6–12 mg/day rivastigmine group had a statistically significantly higher incidence than the placebo group, with rates of 19 and 8%, respectively. Agid and colleagues[59] reported rates of 4% for the 4 mg/day group, 13% for the 6 mg/day group and 6% for the placebo group. The study comparing twice and three times daily groups with placebo reported incidence rates of 16, 20 and 4%, respectively.[60]

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Serious adverse events

Two of the four included published studies commented on the incidence of serious adverse events. Thirteen serious adverse events occurred in the study by Forette and colleagues,[60] but only two during the titration phase and two during the maintenance phase were considered by the investigators to be possibly related to study medication. Rösler and colleagues[58] reported rates of ~18% in all groups. **[Commercial/academic confidential information removed]**

Withdrawals due to adverse events

All four published studies reported withdrawals due to adverse events (*Table 23*), and these varied considerably. Placebo group rates ranged from 4 to 7.2%, and 7–28.6% of treatment participants withdrew owing to adverse events. None of the studies reported *p*-values, but Rösler and colleagues[58] commented that the incidence rate of 23% for the 6–12 mg/day rivastigmine group was statistically significantly higher than the 7% rate reported for the placebo group. **[Commercial/academic confidential information removed]**

Withdrawals unrelated to adverse events varied between included trials. In two published[58,60] **[Commercial/academic confidential information removed]** higher proportions withdrew in the intervention groups than in the placebo groups.

This appeared generally to be related to higher doses of rivastigmine, but, it was not tested for statistical significance in the two published trials. **[Commercial/academic confidential information removed]** Two trials showed no difference in the rates of withdrawals and one[57] demonstrated a higher proportion in the placebo group, but these were not tested for statistical significance. Very few deaths were reported. All data relating to withdrawals and deaths can be found for the individual studies in Appendix 8.

Summary

- Four published RCTs on the effectiveness of rivastigmine met the inclusion criteria for this review. All four trials were sponsored by the manufacturer. The quality of reporting was generally poor for two of these. None of the trials lasted longer than 26 weeks. Only two of the trials reported an adequate method of randomisation, and only one of these clearly reported concealment of allocation. The other three may therefore have been subject to selection bias, which would affect interpretation of the results. Withdrawals were not adequately described by two of the trials, and attrition bias may therefore affect the results of these. None of the trials reported assessor blinding adequately, so measurement bias may need to be taken into consideration when discussing the trials' findings.
- Two unpublished studies were included in the review. **[Commercial/academic confidential information removed]**
- Statistically significant differences between the 6–12 mg/day treatment groups (mean dose ~10 mg/day) and placebo were reported by two of three published trials which reported ADAS-cog and MMSE. No statistically significant effects were seen in the low-dose treatment groups in these studies. Forette and colleagues[60] found that participants receiving twice daily doses of rivastigmine scored statistically significantly better on the Wechsler logical memory test than did those receiving the drug three times daily. However, sample sizes were very low (<30 participants in each group) and this study presented no information on power calculations.
- The unpublished studies **[commercial/academic confidential information removed]**.
- The unpublished studies **[commercial/academic confidential information removed]**.
- Both of the published studies which included CIBIC-plus as a global outcome measure reported a statistically significant improvement in high-dose participants (6–12 mg/day) compared with placebo participants. One study also reported a statistically significantly greater proportion of 'responders' among participants treated with rivastigmine compared against placebo participants. Another study reported that a greater proportion of high-dose rivastigmine participants than placebo participants had a 'successful' CIGIC assessment, i.e. scoring 1 or 2 on the scale. Two trials found a statistically significant improvement on the GDS measure in participants treated with 6–12 mg/day of rivastigmine compared with placebo participants.
- Two published studies reported the PDS as a functional outcome measure. One of these found a statistically significant improvement in participants treated with 6–12 mg/day rivastigmine compared with placebo, and the other reported that a statistically significantly higher percentage of these high-dose participants than placebo participants showed an improvement of at least 10%.
- The unpublished studies **[commercial/academic confidential information removed]**.
- All published trials showed a higher incidence of adverse events for participants treated in rivastigmine groups compared with placebo. Levels of nausea and vomiting were particularly high among participants treated with the higher dose of rivastigmine (6–12 mg/day). One study also found a statistically significantly higher incidence of these side-effects in the low-dose (1–4 mg/day) group compared with placebo. Dizziness and headache were also more widely reported by high-dose participants than by placebo participants.
- Both unpublished trials **[commercial/academic confidential information removed]**.
- Both unpublished trials **[commercial/academic confidential information removed]**.

Galantamine

Quantity and quality of research

Six published **[commercial/academic confidential information removed]** RCTs assessing the clinical effectiveness of galantamine for AD met the inclusion criteria for the systematic review and can be seen in *Table 24*.[61–66] Four published RCTs assessed several different doses of galantamine with participants in different arms of the RCTs receiving doses ranging from 8 to 36 mg/day.[61,63–65]

TABLE 24 *Characteristics of included studies for galantamine*

Study	Methods	Participants	Outcomes
[Commercial/academic confidential information removed]			
Raskind *et al.*, 2000[61]	*Design*: multicentre, double-blind RCT *Interventions*: 1. Galantamine 24 mg/day 2. Galantamine 32 mg/day 3. Placebo *Number of centres*: 33 *Duration of treatment*: 6 months *Sponsor*: Janssen Research Foundation	*Inclusion criteria*: probable AD (NINCDS-ADRDA); MMSE score of 11–24; ≥ 12 on ADAS-cog *Numbers*: 636 randomised 1. 212 to 24 mg/day 2. 211 to 32 mg/day 3. 213 to placebo *Mean age*: 1. 75.9 ± 0.5 2. 75.0 ± 0.6 3. 75.3 ± 0.6	*Primary*: • ADAS-cog/11 • CIBIC-plus *Secondary*: • ADAS-cog/13 • Proportion of responders on ADAS-cog/11 • DAD • Adverse events
Rockwood *et al.*, 2001[62]	*Design*: multicentre, double-blind RCT *Interventions*: 1. Galantamine 24–32 mg/day 2. Placebo *Number of centres*: 43 *Duration of treatment*: 3 months *Sponsor*: Janssen Research Foundation	*Inclusion criteria*: probable AD (NINCDS-ADRDA); MMSE score of 11–24 and ≥ 2 on ADAS-cog. *Numbers*: 386 randomised. 1. 261 to galantamine (72 final dose 24 mg/day, 103 final dose 32 mg/day) 2. 125 to placebo *Mean age*: 1. 75.2 (0.45) 2. 74.6 (0.68)	*Primary*: • ADAS-cog/11 • CIBIC-plus *Secondary*: • Expanded ADAS-cog/13 • Proportions of responders (defined as improvements in ADAS-cog/11 ≥ 4 points from baseline) • NPI • DAD • Adverse events
Tariot *et al.*, 2000[63] Cummings *et al.*, 2004[67]	*Design*: multicentre, double-blind RCT *Interventions*: 1. Galantamine 8 mg/day 2. Galantamine 16 mg/day 3. Galantamine 24 mg/day 4. Placebo *Number of centres*: 5 *Duration of treatment*: 5 months *Sponsor*: Janssen Research Foundation	*Inclusion criteria*: probable AD (NINCDS-ADRDA); MMSE score 10–22, ADAS-cog score of ≥ 18 (from standard 11-item cognitive subscale). *Numbers*: 978 randomised 1. 140 to 8 mg/day 2. 279 to 16 mg/day 3. 273 to 24 mg/day 4. 286 to placebo *Mean age*: 1. 76.0 ± 0.6 2. 76.3 ± 0.5 3. 77.7 ± 0.4 4. 77.1 ± 0.5	*Primary*: • ADAS-cog/11 • CIBIC-plus *Secondary*: • Responders on ADAS-cog (≥ 4 points relative to baseline) • Proportion improved by ≥ 7 points on the ADAS-cog • AD Cooperative Study Activities of Daily Living inventory (ADCS/ADL) • NPI • Adverse events
Wilcock *et al.*, 2000[64]	*Design*: multicentre, double-blind RCT *Interventions*: 1. Galantamine 24 mg/day 2. Galantamine 32 mg/day 3. Placebo *Number of centres*: 86 *Duration of treatment*: 6 months *Sponsor*: Janssen Research Foundation	*Inclusion criteria*: probable AD (NINCDS-ADRDA); MMSE score 11–24 and a score of ≥ 12 on ADAS-cog/11 scale *Numbers*: 653 randomised: 1. 220 to 24 mg/day 2. 218 to 32 mg/day 3. 215 to placebo *Mean age*: 1. 71.9 (8.3) 2. 72.1 (8.6) 3. 72.2 (7.6)	*Primary*: • ADAS-cog/11 • CIBIC-plus *Secondary*: • ADAS-cog/13 • Proportion improving on ADAS-cog/11 (≥ 0 and ≥ 4 points) • DAD scale • Adverse events

continued

TABLE 24 *Characteristics of included studies for galantamine (cont'd)*

Study	Methods	Participants	Outcomes
Wilkinson and Murray, 2001[65]	*Design*: multicentre, double-blind RCT *Number of centres*: 8 *Interventions*: 1. Galantamine 18 mg/day 2. Galantamine 24 mg/day 3. Galantamine 36 mg/day 4. Placebo *Duration of treatment*: 12 weeks *Sponsor*: Shire Pharmaceuticals	*Inclusion criteria*: >45 years old; probable AD (NINCDS-ADRDA and DSM-III-R); MMSE 13–24 Numbers: 285 randomised 1. 88 to 8 mg/day 2. 56 to 24 mg/day 3. 54 to 36 mg/day 4. 87 to placebo *Mean age*: 18 mg/day 72.7 ± 0.9, 24 mg/day 72.9 ± 1.1, 36 mg/day 75.4 ± 1.0, placebo 74.2 ± 0.9	*Primary*: • ADAS-cog *Secondary*: • CGIC • PDS-1 • Adverse events
Wilkinson *et al*., 2000[66]	*Design*: multicentre, double-blind RCT *Interventions*: 1. Galantamine 24–32 mg/day 2. Placebo *Number of centres*: 43 *Duration of treatment*: 3 months *Sponsor*: not reported	*Inclusion criteria*: probable AD (NINCDS-ADRDA); MMSE 11–24 and ≥12 on the ADAS-cog *Numbers*: 386 randomised 1. 261 to galantamine 2. 125 to placebo *Mean age*: 1. 75.2 (0.45) 2. 74.6 (0.68)	*Primary*: • ADAS-cog • CIBIC-plus • DAD scale *Secondary*: • Adverse events

The other two published RCTs varied the dose participants could receive to between 24 and 32 mg/day.[62,66] **[Commercial/academic confidential information removed]** The duration of treatment was short with three published RCTs treating participants for 3 months,[62,65,66] one for 5 months[63,67] and two for 6 months.[61,64] **[Commercial/academic confidential information removed]** Samples randomised into the different arms of the trials ranged from 285 participants[65] to 978 participants.[63,67] Five published RCTs[61–65] calculated the sample size required or study power and three RCTs were able to recruit adequate samples.[61,62,64] **[Commercial/academic confidential information removed]** Although the studies provided slightly different criteria for defining their patient groups, all studies included participants with a diagnosis of probable AD using the NINCDS-ADRDA criteria, an MMSE score ranging between 10 and 24 and had a mean age >70 years.[61–66] Clinical effectiveness was assessed using several different outcome measures, although the ADAS-cog and CIBIC-plus were the primary outcomes assessed in most studies. Five published **[commercial/academic confidential information removed]** RCTs used ADAS-cog as the primary outcome measure to calculate the appropriate sample size.[61–65]

The methodological quality and the quality of reporting in the studies assessing galantamine varied (*Table 25*). Five published RCTs[61–65] **[commercial/academic confidential information removed]** adequately described the method of allocation of participants to the different arms of the RCTs and for one RCT the method of randomisation was unknown.[66] Three published studies[62,64,65] **[commercial/academic confidential information removed]** adequately described the concealment of allocation. Three studies did not adequately discuss concealment of allocation and the method was considered to be unknown.[61,63,66] Seven studies reported baseline characteristics of the participants included in the different arms of the trials and adequately discussed the use of eligibility criteria for pre-specifying samples. As a result, three published RCTs[62,64,65] **[commercial/academic confidential information removed]** appeared to limit adequately the possible effects of selection bias.

Blinding of participants, care providers and assessors helps to guard against systematic differences in ascertainment of outcomes for the different groups. Blinding of assessors was adequately described in one RCT,[61] with the remaining five published[62–66] **[commercial/academic confidential information removed]** RCTs providing no or inadequate discussion of blinding of assessors. Blinding of the care provider was adequate in four published[61,63–65] **[commercial/academic confidential information removed]** RCTs, partial in one RCT[62] and inadequate in one RCT.[66] In contrast, blinding of

TABLE 25 *Quality assessment table for galantamine*

Study	Randomisation	Concealment of allocation	Baseline characteristics	Eligibility	Blinding of assessors	Care provider blinding	Patient blinding	Reporting outcomes	ITT analysis	Withdrawals explained
Raskind *et al.*[61]	Ad	Un	Rep	Ad	Ad	Ad	Ad	Ad	In	Ad
Rockwood *et al.*[62]	Ad	Ad	Rep	Ad	Par	Par	Ad	Ad	In	Ad
Tariot *et al.*[63,67]	Ad	Un	Rep	Ad	Un	Ad	Ad	Ad	In	Ad
Wilcock *et al.*[64]	Ad	Ad	Rep	Ad	Par	Ad	Ad	Ad	In	Ad
Wilkinson and Murray[65]	Ad	Ad	Rep	Ad	Un	Ad	Ad	Ad	In	Ad
Wilkinson *et al.*[66]	Un	Un	Rep	Ad	Un	In	In	Ad	In	In
[Commercial/academic confidential information removed]										

Ad, adequate; In, inadequate; Par, partial; Rep, reported; Un, unknown.

participants to intervention was adequate in five published[61–65] **[commercial/academic confidential information removed]** RCTs and inadequate in one RCT.[66] Only three published[61,63,65] **[commercial/academic confidential information removed]** RCTs provided adequate information to judge that they were actually double-blind RCTs, with only one RCT stating that it also blinded assessors.[61] As a consequence, the remaining studies may be affected to different degrees by measurement bias.

All six published RCTs adequately reported primary outcomes, including point estimates and measures of variability.[61–66] **[Commercial/academic confidential information removed]** Withdrawals or exclusion of participants from the different groups may lead to systematic differences (attrition bias), and it is important that these are accounted for in the subsequent analysis. No RCTs adequately reported results through an ITT analysis, and only five RCTs provided an adequate explanation of withdrawals.[61–65] As a consequence, no RCTs were considered to have guarded against the effects of attrition bias. Results will be reported using the most rigorous approach presented within the RCTs, usually ITT (LOCF). Where a different method of analysis is used, it will be outlined.

Assessment of clinical effectiveness

Cognitive outcome measures

ADAS-cog

All six published **[commercial/academic confidential information removed]** RCTs assessed the clinical effectiveness of galantamine compared with placebo using either the ADAS-cog 11-item or 13-item scale, presenting outcomes as the mean (and standard error) change from baseline (see *Table 26*). Rockwood and colleagues[62] found a statistically significant difference in the mean change from baseline on the ADAS-cog 11-item scale (difference 1.6 points), with the group receiving galantamine 24–32 mg/day experiencing an improvement compared to a deterioration for the placebo group over the 3 months of the study. A statistically significant difference (difference 1.8 points) was also reported on the ADAS-cog 13-item scale favouring the galantamine 24–32 mg/day group compared with the placebo group. In another comparison of galantamine 24–32 mg/day with placebo, Wilkinson and colleagues[66] found a similar statistically significant difference in the mean change from baseline on the ADAS-cog showing benefit for the group receiving galantamine 24–32 mg/day compared with placebo (difference 1.7 points). **[Commercial/academic confidential information removed]**

Raskind and colleagues[61] and Wilcock and colleagues[64] compared the effects of two different doses of galantamine, 24 and 32 mg/day, with placebo during the 6-month study periods. Raskind and colleagues[61] reported a statistically significant improvement in the mean change from baseline on the ADAS-cog for the participants receiving galantamine 24 mg/day (difference 1.9 points) and 32 mg/day (difference 3.4 points) compared with those receiving placebo, who experienced a decline. It should be noted that Raskind and colleagues[61] reported the change

TABLE 26 *ADAS-cog for galantamine: all mean (SEM) change from baseline*

Rockwood et *al*.[62]			
ADAS-cog/11			
Galantamine 24–32 mg/day (*n* = 260)	**Placebo (*n* = 125)**		***p*-Value vs placebo**
–0.9 (0.31)**	0.7 (0.47)		**$p < 0.01$
Wilkinson et *al*.[66]			
Galantamine 24–32 mg/day (*n* = 239)	**Placebo (*n* = 120)**		***p*-Value vs placebo**
–1.1 (0.33)	0.6 (0.45)		$p < 0.01$
[Commercial/academic confidential information removed]			
Raskind et *al*.[61]			
1. Galantamine 24 mg/day (*n* = 202)	**2. Galantamine 32 mg/day (*n* = 197)**	**3. Placebo (*n* = 207)**	***p*-Value vs placebo**
–1.9[a] (0.36)	–1.4 (0.44)	2.0 (0.45)	1. $p < 0.001$ 2. $p < 0.001$
[a] Incorrectly reported in study as +1.9.			
Wilcock et *al*.[64]			
1. Galantamine 24 mg/day (*n* = 220)	**2. Galantamine 32 mg/day (*n* = 217)**	**3. Placebo (*n* = 215)**	**Treatment difference (95% CI), *p*-Value vs placebo**
–0.5 (0.38)	–0.8 (0.43)	2.4 (0.41)	1. 2.9 (1.6 to 4.1) $p < 0.001$ 2. 3.1 (1.9 to 4.4) $p < 0.001$
Tariot et *al*.[63,67]			
1. Galantamine 8 mg/day (*n* = 126)	**2. Galantamine 16 mg/day (*n* = 253)**	**3. Galantamine 24 mg/day (*n* = 253)**	**4. Placebo (*n* = 255)**	***p*-Value vs placebo**
0.4 (0.52)	–1.4 (0.35)[b]	–1.4 (0.39)[b]	1.7 (0.39)	1. $p < 0.001$ 2. $p < 0.001$
[b] $p < 0.01$ versus 8 mg/day group.				
Wilkinson and Murray[65] ***(Scores for galantamine 24 and 32 mg/day were incorrectly reported in the study as being plus rather than minus)***				
1. Galantamine 18 mg/day (*n* = 81)	**2. Galantamine 24 mg/day (*n* = 55)**	**3. Galantamine 36 mg/day (*n* = 51)**	**4. Placebo (*n* = 82)**	***p*-Value vs placebo**
–0.1 (0.7)	–1.4 (0.9)	–0.7 (0.7)	1.6 (0.7)	2. $p < 0.01$ 3. $p = 0.08$

from baseline on the mean ADAS-cog for participants on galantamine 24 mg/day as +1.9 points, stating it as a statistically significant improvement consistent with the group receiving 32 mg/day. It was assumed that this was an error and should be negative as was the case for other outcomes reported for the 24 mg/day group and for the 32 mg/day group on ADAS-cog. Wilcock and colleagues[64] found a similar statistically significant improvement on ADAS-cog for participants receiving galantamine 24 mg/day (difference 2.9 points) and 32 mg/day (difference 3.2 points) compared with a worsening for participants on placebo.

Tariot and colleagues[63] compared three doses of galantamine with placebo over the 5 months study duration, 8, 16 and 24 mg/day. Participants receiving 8 mg/day galantamine experienced a slight deterioration in their mean ADAS-cog score from baseline, whereas participants receiving either 16 or 24 mg/day galantamine improved. In contrast, the ADAS-cog score for participants on placebo deteriorated from baseline. Changes in ADAS-cog from baseline for participants receiving 16 or 24 mg/day differed statistically significantly compared with participants receiving 8 mg/day (difference both doses 1.8 points) or placebo (difference both doses 3.1 points).

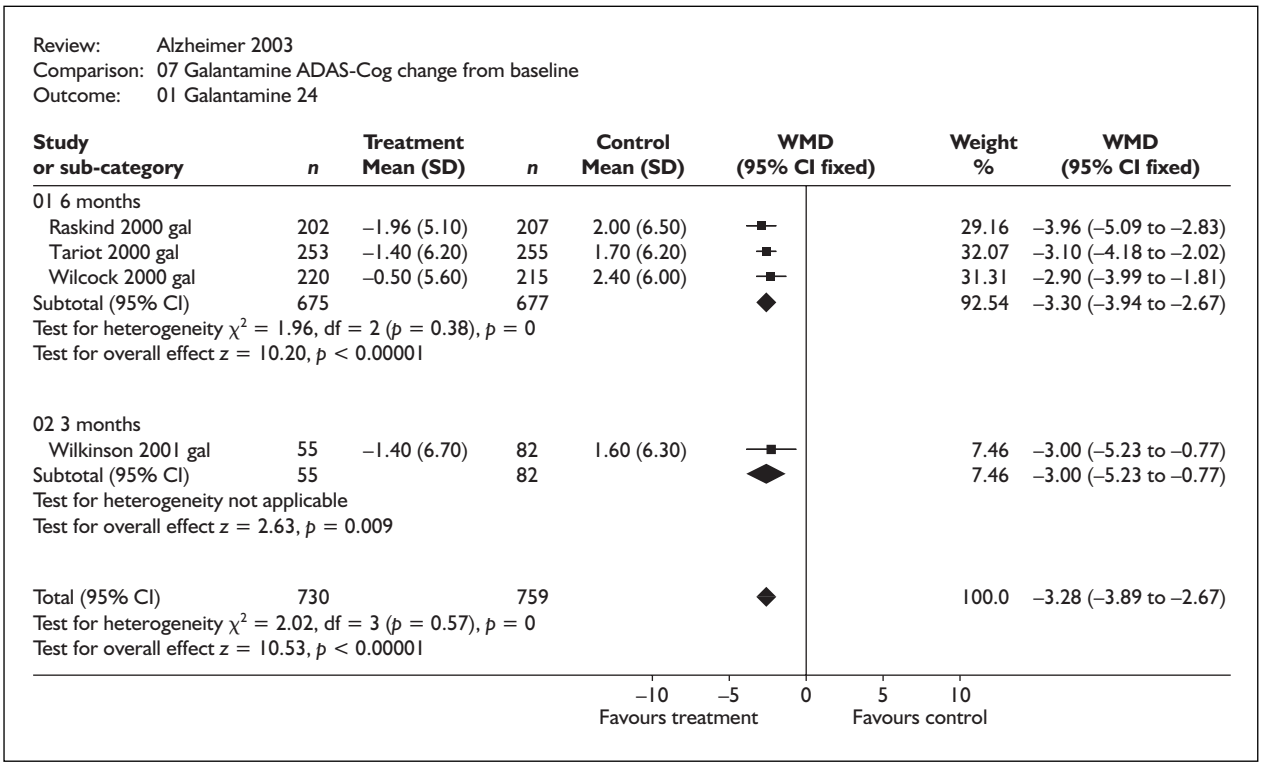

FIGURE 13 *ADAS-cog change from baseline with galantamine 24 mg*

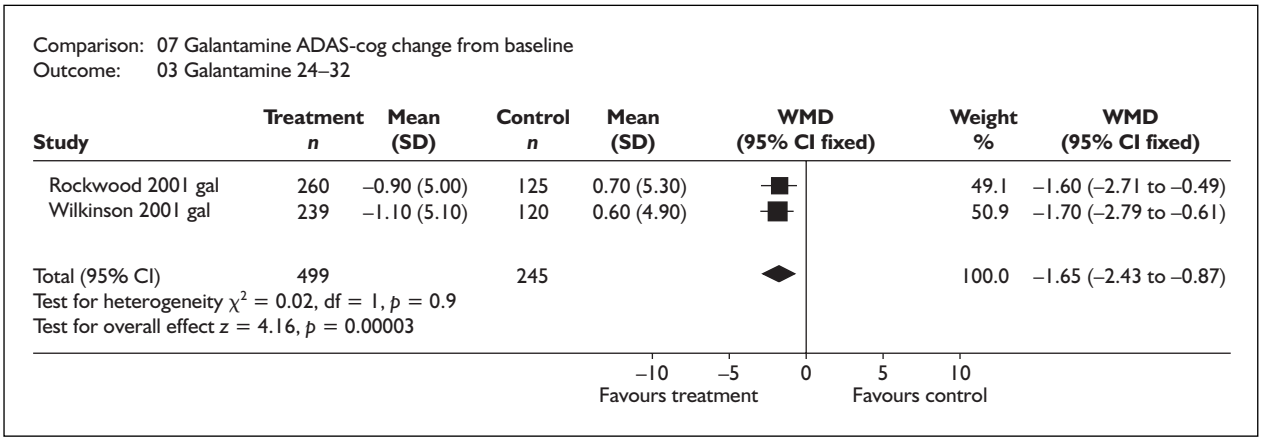

FIGURE 14 *ADAS-cog change from baseline with galantamine 24–32 mg*

In a comparison of three doses of galantamine with placebo over a 3-month period, Wilkinson and Murray[65] found that participants receiving either 18 mg/day (difference 1.7 points), 24 mg/day (difference 3.0 points) or 36 mg/day (difference 2.3 points) galantamine experienced an improvement on the ADAS-cog scale, whereas those on placebo deteriorated. Only participants receiving 24 mg/day galantamine improved statistically significantly compared with placebo.

The benefits of treatment with galantamine compared with placebo on the ADAS-cog scale were shown through meta-analyses, using fixed and random effects models, for different doses and lengths of study. The fixed-effect model for 24 mg/day galantamine compared with placebo showed a weighted mean difference on ADAS-cog favouring galantamine at 3 months [WMD –3.00 (95% CI: –5.23 to –0.77)] and 6 months follow-up [WMD –3.28 (95% CI: –3.89 to –2.67)] (see

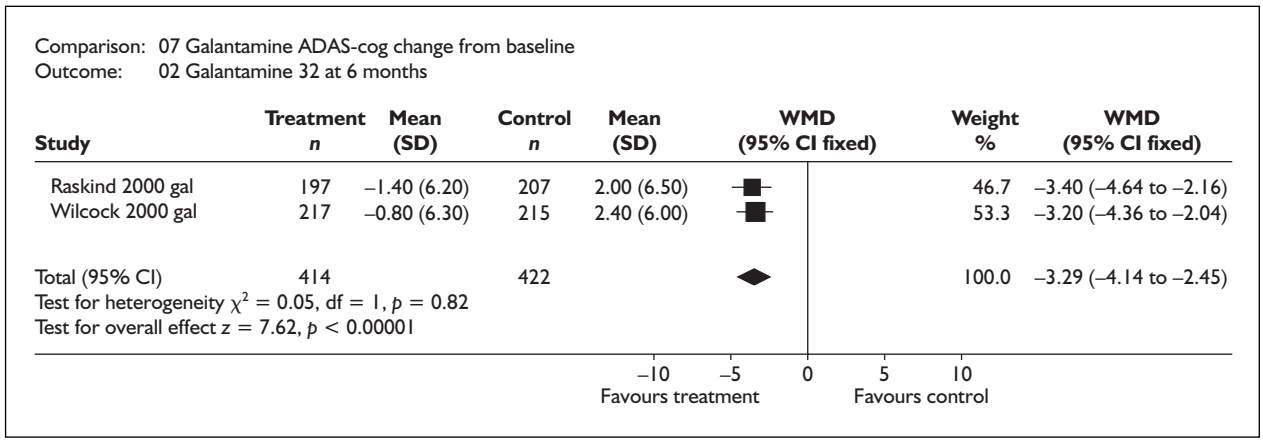

FIGURE 15 *ADAS-cog change from baseline with galantamine 32 mg*

Figure 13). Similarly, the fixed-effect models for 24–32 mg/day compared with placebo [WMD –1.65 (95% CI: –2.43 to –0.87)] and for 32 mg/day galantamine compared with placebo [WMD –3.29 (95% CI: –4.14 to –2.45)] favoured galantamine at 6 months follow-up (*Figures 14* and *15*). Use of the random effects models resulted in limited change to the outcomes of the meta-analysis and none of the models were affected by heterogeneity.

Cognitive responders on ADAS-cog

Three RCTs reported the proportion of participants who were responders to treatment with at least a 4-point improvement on the ADAS-cog scale (*Table 27*). Rockwood and colleagues[62] reported that a higher proportion of participants on galantamine 24–32 mg/day were responders to treatment compared with those on placebo (difference 6.3%). Wilcock and colleagues[64] noted that statistically significantly more participants on galantamine 24 mg/day (difference 14%) and 32 mg/day (difference 17%) were considered to be responders to treatment on ADAS-cog compared with participants receiving placebo. Similar differences in the proportion of responders to treatment were found by Tariot and colleagues with statistically significantly more participants on 16 mg/day (difference 16%) and 24 mg/day (difference 17.4%) achieving a 4-point or more improvement on ADAS-cog/11 scale compared with participants on placebo.[63]

Summary: galantamine appears to confer a statistically significant benefit to participants compared with placebo on the cognitive outcome ADAS-cog.

Global outcome measures

CIBIC-plus

Five published **[commercial/academic confidential information removed]** RCTs assessed the clinical effectiveness of galantamine using the CIBIC-plus outcome measure, reporting either the proportion of participants within each category[61,62,64,66] or the proportion of responders (*Table 28*).[63]

A comparison of 24–32 mg/day galantamine with placebo by Rockwood and colleagues[62] found that a greater proportion of participants receiving galantamine improved on the CIBIC-plus scale compared with those on placebo, with statistically significantly more reporting a minimal (difference 4.1%) or moderate (difference 2.0%) improvement. In contrast, statistically significantly more participants in the placebo group experienced minimal (difference 11.7%) or moderate (difference 4.1%) worsening of their condition compared with those in the galantamine group. Wilkinson and colleagues[66] reported similar differences, with participants receiving 24–32 mg/day galantamine reporting statistically significant benefit on the CIBIC-plus outcome measure compared with participants on placebo. Statistically significant differences were also identified by Raskind and colleagues[61] and Wilcock and colleagues[64] when comparing the doses of 24 and 32 mg/day galantamine with placebo. Raskind and colleagues[61] reported that statistically significantly more participants receiving either 24 or 32 mg/day galantamine showed marked, moderate or minimal improvement on CIBIC-plus compared with placebo. In addition, statistically significantly more placebo participants worsened minimally, moderately or markedly than participants on either 24 or 32 mg/day galantamine. Comparison between the two doses of galantamine showed slight benefit for those participants receiving 24 mg/day, although the differences were not statistically significant. Although Wilcock and colleagues[64] found comparable benefits for participants receiving 24 and 32 mg/day

TABLE 27 *ADAS-cog: responders for galantamine*

Rockwood *et al.*[62]				
No. (%) ADAS-cog/11 responders ≥ 4 points improvement				
Galantamine 24–32 mg/day (*n* = 258)		**Placebo (*n* = 123)**		***p*-Value vs placebo**
73 (28.3)		27 (22.0)		ns
Wilcock *et al.*[64]				
1. Galantamine 24 mg/day (*n* = 220)	**2. Galantamine 32 mg/day (*n* = 217)**	**3. Placebo (*n* = 215)**		**Treatment difference (95% CI), *p*-Value vs placebo**
No. (%) with ≥ 0 points improvement				
138 (63)	130 (60)	88 (41)		1. 21.5 (12.0 to 31.0) $p < 0.001$ 2. 19.5 (10.0 to 29.0) $p < 0.001$
No. (%) with ≥ 4 points improvement				
64 (29)	70 (32)	32 (15)		1. 14.0 (6.0 to 22.0) $p < 0.001$ 2. 17.0 (9.0 to 25.0) $p < 0.001$
Tariot *et al.*[63,67]				
1. Galantamine 8 mg/day (*n* = 126)	**2. Galantamine 16 mg/day (*n* = 253)**	**3. Galantamine 24 mg/day (*n* = 253)**	**4. Placebo (*n* = 255)**	***p*-Value vs placebo**
ADAS-cog/11 responders ≥ 4 points improvement (%)				
Not reported	35.6	37.0	19.6	1. $p < 0.001$ 2. $p < 0.001$
Proportion participants, on ADAS-cog, improved ≥ 7 points relative to baseline (%)				
Not reported	15.9	22.3	7.6	1. $p < 0.01$ 2. $p < 0.01$

TABLE 28 *CIBIC-plus for galantamine: all* n *(%) unless stated otherwise*

Rockwood *et al.*[62]		
Galantamine 24–32 mg/day (*n* = 248)	**Placebo (*n* = 124)**	***p*-Value vs placebo**
1 = markedly improved 1 (0.4)	1 = markedly improved 0 (0)	
2 = moderately improved 7 (2.8)**	2 = moderately improved 1 (0.8)	**$p < 0.01$
3 = minimally improved 56 (22.6)**	3 = minimally improved 23 (18.5)	**$p < 0.01$
4 = no change 132 (53.2)**	4 = no change 54 (43.5)	**$p < 0.01$
5 = minimally worsened 43 (17.3)**	5 = minimally worsened 36 (29.0)	**$p < 0.01$
6 = moderately worsened 8 (3.2)**	6 = moderately worsened 9 (7.3)	**$p < 0.01$
7 = markedly worsened 1 (0.4)	7 = markedly worsened 1 (0.8)	
Wilkinson *et al.*[66]		
Galantamine 24–32 mg/day (*n* = 240)	**Placebo (*n* = 123)**	***p*-Value vs placebo**
1 = markedly improved 0.4	1 = markedly improved 0	
2 = moderately improved 2.9	2 = moderately improved 0.8	
3 = minimally improved 22.1	3 = minimally improved 18.7	Overall $p < 0.01$
4 = no change 55.4	4 = no change 43.1	
5 = minimally worsened 16.7	5 = minimally worsened 29.3	
6 = moderately worsened 2.5	6 = moderately worsened 7.3	
7 = markedly worsened 0	7 = markedly worsened 0.8	

continued

TABLE 28 *CIBIC-plus for galantamine: all* n *(%) unless stated otherwise (cont'd)*

Raskind et *al.*[61]

1. Galantamine 24 mg/day (*n* = 186)	2. Galantamine 32 mg/day (*n* = 171)	3. Placebo (*n* = 196)	*p*-Value vs placebo
1 = markedly improved 3 (1.6)	1 = markedly improved 2 (1.2)	1 = markedly improved 1 (0.5)	1. $p < 0.01$ 2. $p < 0.05$
2 = moderately improved 6 (3.2)	2 = moderately improved 4 (2.3)	2 = moderately improved 7 (3.6)	1. $p < 0.01$ 2. $p < 0.05$
3 = minimally improved 28 (15.1)	3 = minimally improved 21 (12.3)	3 = minimally improved 19 (9.7)	1. $p < 0.01$ 2. $p < 0.05$
4 = no change 99 (53.2)	4 = no change 91 (53.2)	4 = no change 84 (42.9)	1. $p < 0.01$ 2. $p < 0.05$
5 = minimally worsened 36 (19.4)	5 = minimally worsened 43 (25.1)	5 = minimally worsened 60 (30.6)	1. $p < 0.01$ 2. $p < 0.05$
6 = moderately worsened 10 (5.4)	6 = moderately worsened 9 (5.3)	6 = moderately worsened 24 (12.2)	1. $p < 0.01$ 2. $p < 0.05$
7 = markedly worsened 4 (2.2)	7 = markedly worsened 1 (0.6)	7 = markedly worsened 1 (0.5)	1. $p < 0.01$ 2. $p < 0.05$

Wilcock et *al.*[64]

1. Galantamine 24 mg/day (*n* = 206)	2. Galantamine 32 mg/day (*n* = 198)	3. Placebo (*n* = 203)	*p*-Value vs placebo (95% CI)
1 = much improved 0	1 = much improved 0	1 = much improved 0	
2 = moderately improved 7 (3)	2 = moderately improved 9 (5)	2 = moderately improved 1 (0.5)	
3 = minimally improved 29 (14)*	3 = minimally improved 39 (20)**	3 = minimally improved 32 (16)	*$p < 0.05$; **$p < 0.001$ (unclear if overall or just category 3)
4 = no change 91 (44)	4 = no change 82 (41)	4 = no change 68 (33)	
5 = minimally worsened 57 (28)	5 = minimally worsened 54 (27)	5 = minimally worsened 68 (33)	
6 = moderately worsened 17(8)	6 = moderately worsened 14 (7)	6 = moderately worsened 32 (16)	
7 = much worsened 5 (2)	7 = much worsened 1 (1)	7 = much worsened 2 (1)	

[Commercial/academic confidential information removed]

Tariot et *al.*[63,67] Proportion of responders

1. Galantamine 8 mg/day (*n* = 126)	2. Galantamine 16 mg/day (*n* = 253)	3. Galantamine 24 mg/day (*n* = 253)	4. Placebo (*n* = 255)	*p*-Value vs placebo
68 (53)	169 (66)[a]	162 (64)[b]	128 (49)	1. $p < 0.001$ 2. $p < 0.001$

[a] $p < 0.05$ and [b] $p < 0.01$ versus 8 mg/day galantamine group.

galantamine compared with placebo, the differences were less marked. **[Commercial/academic confidential information removed]**

In a comparison of 8, 16 and 24 mg/day galantamine with placebo, Tariot and colleagues[63] reported that statistically significantly higher proportions of participants receiving 16 mg/day (difference: placebo 17%; 8 mg/day 13%) or 24 mg/day (difference: placebo 15%; 8 mg/day 11%) remained stable or improved (responders) compared with placebo or 8 mg/day.[63]

Wilkinson and Murray[65] reported the differences in the proportion of participants who were classified as either much improved, improved, no change, worse or much worse on the CGIC scale. Although participants on 18 and 36 mg/day galantamine were more likely to have improved/much improved and those on placebo more likely to be worse/much worse, the differences were not statistically significant.

A meta-analysis, using fixed- and random-effects models, of the proportion of responders on the

CIBIC-plus scale showed the benefits of treatment with galantamine compared with placebo for different doses and lengths of study, although these were not statistically significant (see *Figures 16–18*). The fixed-effect model for 24–32 mg/day galantamine compared with placebo showed an OR favouring galantamine at 3 months [OR 1.43 (95% CI: 0.98 to 2.08)] and for galantamine 24 mg/day compared to placebo at 6 months follow-up [OR 1.29 (95% CI: 0.89 to 1.88)]. Similarly, the OR from the fixed-effect models for 32 mg/day galantamine compared with

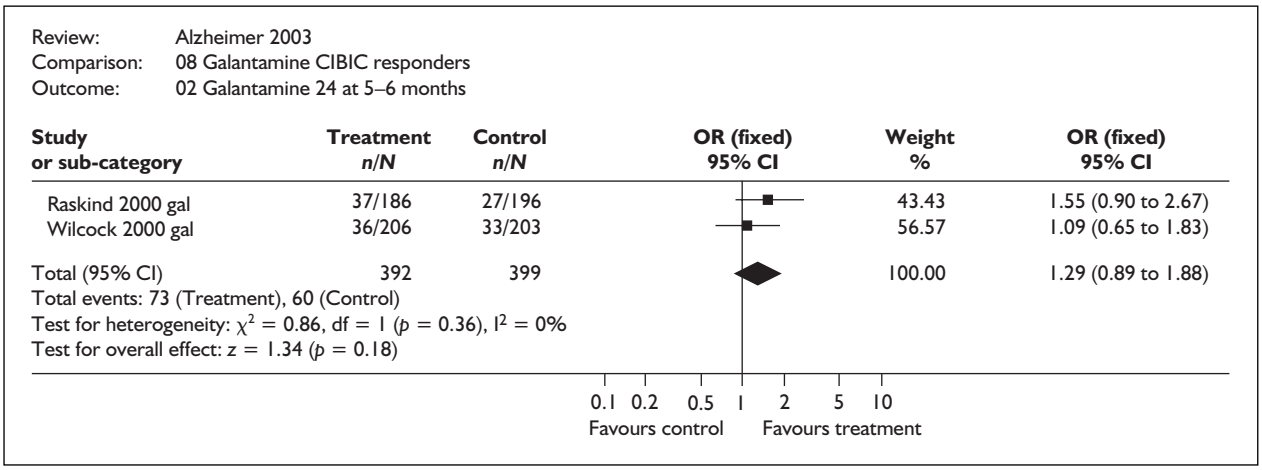

FIGURE 16 *CIBIC-plus responders with galantamine 24 mg*

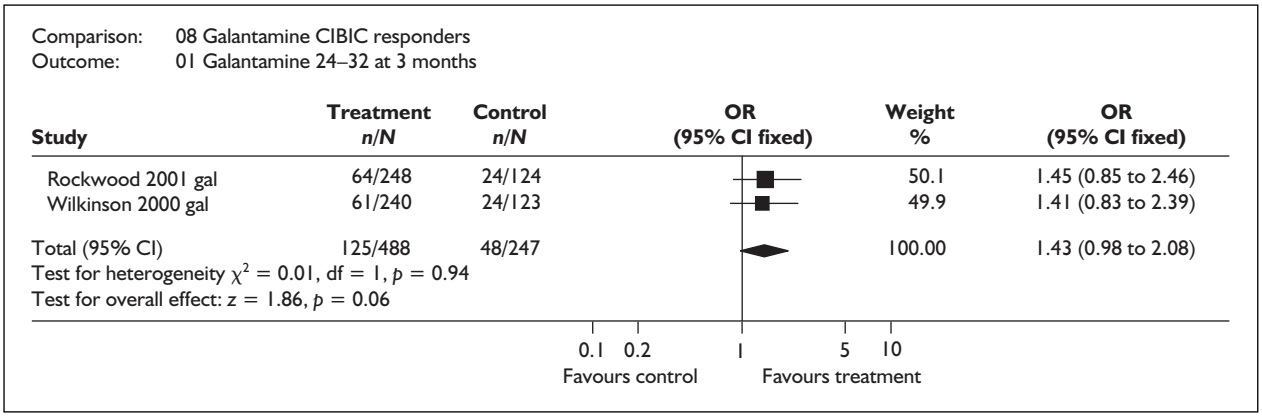

FIGURE 17 *CIBIC-plus responders with galantamine 24–32 mg*

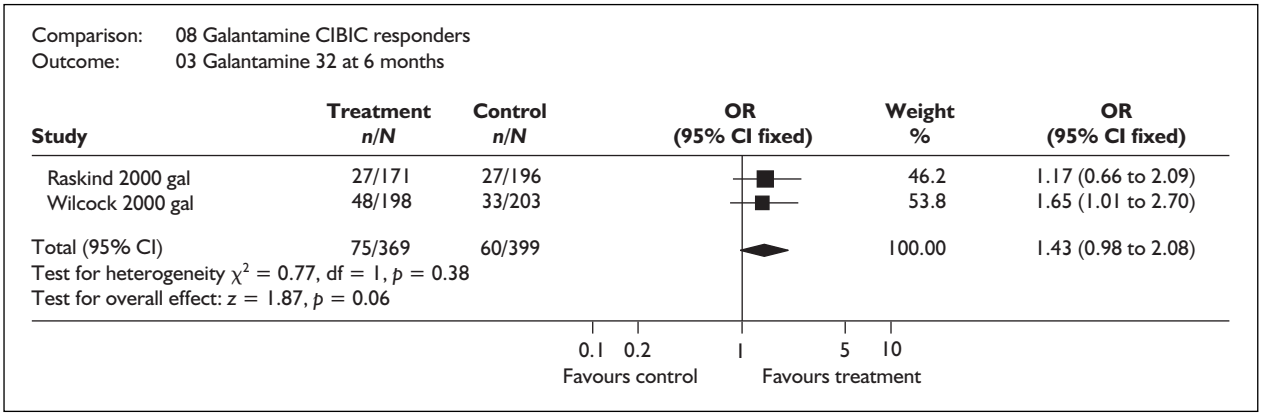

FIGURE 18 *CIBIC-plus responders with galantamine 32 mg*

placebo [OR 1.43 (95% CI: 0.98 to 2.08)] favoured galantamine at 6 months follow-up. Use of the random effects models resulted in limited change to the outcomes of the meta-analysis and none of the models were affected by heterogeneity.

Summary: in individual studies higher proportions of participants on galantamine improved on CIBIC-plus and CGIC compared with participants on placebo, who were likely to deteriorate. When studies were pooled, no statistical significance is noted between treatment groups and placebo.

Function

DAD

Three RCTs assessed changes from baseline on the DAD scale (*Table 29*).[62,64,66] The DAD scale assesses basic and instrumental activities of daily living, initiation, planning and organisation, performance and leisure, scoring people between 0 and 100. Rockwood and colleagues[62] noted that participants in the 24–32 mg/day galantamine group deteriorated statistically significantly less than those in the placebo group (difference 4.1 points). Similarly, Wilkinson and colleagues[66] reported a statistically significantly smaller deterioration on the DAD scale for participants in the 24–32 mg/day galantamine group compared with placebo (difference 4.8 points). Wilcock and colleagues[64] noted a slower deterioration in DAD scores for participants receiving 24 mg/day (difference 2.8 points) or 32 mg/day (difference 3.5 points) galantamine compared with placebo, statistically significantly so for the group receiving 32 mg/day.

ADL

Tariot and colleagues[63] reported mean (SEM) changes from baseline on the Alzheimer's Disease Cooperative Study Activities of Daily Living inventory (ADCS/ADL) for participants receiving 8, 16 and 24 mg/day galantamine and placebo. This outcome measure assesses daily activities in participants, such as using household appliances, choosing clothes to wear, bathing and toileting. Although all participants had deteriorated over the 5 months' duration of the study, it was statistically significantly less for those receiving 16 mg/day [–0.7 (SEM 0.5), $p < 0.001$] and 24 mg/day [–1.5 (SEM 0.6), $p < 0.01$] than placebo [–3.8 (SEM 0.6)]. **[Commercial/academic confidential information removed]**

PDS

Wilkinson and Murray[65] assessed differences in the proportion of participants who were classified as either much improved, improved, no change, worse or much worse on the PDS-1, which is a measure of activities of daily living. Although participants receiving either 18, 24 or 36 mg/day galantamine were less likely to be worse/much worse compared with participants on placebo and that participants receiving either 18 or 24 mg/day were more likely to have improved/much improved compared with participants on placebo or 36 mg/day galantamine, the differences were not statistically significant.

Summary: participants receiving galantamine appeared to suffer less deterioration compared with those on placebo, statistically significantly for doses between 16 and 32 mg/day on the DAD and ADL scales.

TABLE 29 *DAD for galantamine: all mean (SEM) change from baseline*

Rockwood *et al.*[62]			
Galantamine 24–32 mg/day (*n* = 261)		**Placebo (*n* = 125)**	***p*-Value vs placebo**
–1.2 (0.83)		–5.3 (1.17)	$p < 0.01$
Wilkinson *et al.*[66]			
Galantamine 24–32 mg/day (*n* = 239)		**Placebo (*n* = 120)**	***p*-Value vs placebo**
–0.4 (0.76)		–5.2 (1.18)	$p < 0.001$
Wilcock *et al.*[64]			
1. Galantamine 24 mg/day (*n* = 212)	**2. Galantamine 32 mg/day (*n* = 214)**	**3. Placebo (*n* = 210)**	**Treatment difference (95% CI), *p*-value vs placebo**
–3.2 (1.02)	–2.5 (1.07)	–6.0 (1.08)	1. 2.8 (–0.6 to 6.1) $p = 0.1$ 2. 3.4 (0.1 to 6.7) $p < 0.05$

Behaviour and mood

NPI

Two published[62,63,67] **[commercial/academic confidential information removed]** RCTs examined mean (SEM) changes from baseline for NPI and can be seen in *Table 30*. Rockwood and colleagues[62] reported that participants in the 24–32 mg/day arm experienced an improvement on the NPI scale whereas participants on placebo worsened (difference 0.9), but this difference did not reach statistical significance. Tariot and colleagues[63,67] found some improvement on the NPI scale for participants receiving 16 mg/day and no change compared with baseline for those receiving 24 mg/day. Participants receiving 8 mg/day galantamine or placebo experienced deterioration on the NPI scale. Differences in the change in mean NPI score between placebo and the 16 mg/day (difference 2.1) and 24 mg/day (difference 2.0) galantamine groups were statistically significant. **[Commercial/academic confidential information removed]**

Summary: higher doses of galantamine were associated with a statistically significant slowing in the deterioration of participants condition on NPI compared with placebo in one trial. In two trials the slowing of deterioration was not statistically significantly different between those treated with galantamine and those treated with placebo.

Adverse events

All six published **[commercial/academic confidential information removed]** RCTs reported adverse events affecting the different patient groups,[61–66] focusing on the proportion of participants suffering a particular event (see *Table 31*). It was evident that participants receiving galantamine suffered between 2 and 27% more adverse events than those on placebo, with differences tending to reflect a dose–response effect. Nausea affected between 6% (8 mg/day) and 44% (32 mg/day) of galantamine participants compared with between 3 and 13% of placebo participants. Similarly, a higher proportion of participants in the RCTs on galantamine suffered from vomiting (difference range 1–18%), dizziness (difference range 0–10%), anorexia (difference range 3–14%) than participants on placebo. As a consequence, withdrawals due to adverse events

TABLE 30 *NPI for galantamine: all mean (SEM) change from baseline*

Rockwood et *al.*[62]				
Galantamine 24–32 mg/day (*n* = 261)		**Placebo (*n* = 125)**		***p*-Value vs placebo**
–0.4 (0.65)		0.5 (0.64)		ns
Tariot et *al.*[63,67]				
1. Galantamine 8 mg/day (*n* = 129)	**2. Galantamine 16 mg/day (*n* = 255)**	**3. Galantamine 24 mg/day (*n* = 253)**	**4. Placebo (*n* = 262)**	***p*-Value vs placebo**
2.3 (1.0)	–0.1 (0.7)	0.0 (0.8)	2.0 (0.7)	2. $p < 0.05$ 3. $p < 0.05$
[Commercial/academic confidential information removed]				

TABLE 31 *Adverse events for galantamine (note that p-values are not reported unless stated)*

Rockwood et *al.*[62] No. (%) of adverse events occurring at least 5% more with galantamine than placebo		
	Galantamine 24–32 mg/day (*n* = 261)	**Placebo (*n* = 125)**
Nausea	84 (32.2)	14 (11.2)
Dizziness	39 (14.9)	5 (4.0)
Vomiting	38 (14.6)	5 (4.0)
Anorexia	31 (11.9)	3 (2.4)
Somnolence	20 (7.7)	1 (0.8)
Abdominal pain	18 (6.9)	2 (1.6)
Agitation	16 (6.1)	1 (0.8)
Any adverse event	225 (86.2)	79 (63.2)

continued

TABLE 31 *Adverse events for galantamine (note that p-values are not reported unless stated) (cont'd)*

Wilkinson et *al*.[66] Proportion reported by ≥5% of participants (%)

	Galantamine 24–32 mg/day (*n* = 261)	Placebo (*n* = 125)
Nausea	13	Not reported
Vomiting	6	Not reported
Dizziness	5	Not reported
Serious adverse events	8	6

[Commercial/academic confidential information removed]

Raskind et *al*.[61] No. (%) of adverse events occurring at least 5% more with any galantamine than placebo

	Galantamine 24 mg/day (*n* = 212)	Galantamine 32 mg/day (*n* = 211)	Placebo (*n* = 213)
Nausea	79 (37.3)	92 (43.6)	28 (13.1)
Vomiting	44 (20.8)	54 (25.6)	16 (7.5)
Dizziness	29 (13.7)	39 (18.5)	24 (11.3)
Diarrhoea	26 (12.3)	41 (19.4)	21 (9.9)
Anorexia	29 (13.7)	43 (20.4)	12 (5.6)
Weight loss	26 (12.3)	23 (10.9)	10 (4.7)
Abdominal pain	14 (6.6)	23 (10.9)	9 (4.2)
Tremor	11 (5.2)	7 (3.3)	1 (0.5)
Any adverse event	195 (92.0)	195 (92.4)	168 (78.9)

Wilcock et *al*.[64] No. (%) of adverse events occurring at least 5% more with galantamine than placebo

	Galantamine 24 mg/day (*n* = 220)	Galantamine 32 mg/day (*n* = 218)	Placebo (*n* = 215)
Nausea	82 (37)	87 (40)	26 (12)
Vomiting	45 (20)	37 (17)	9 (4)
Diarrhoea	16 (7)	29 (13)	16 (7)
Dizziness	24 (11)	26 (12)	10 (5)
Headache	21 (10)	25 (11)	7 (3)
Anorexia	22 (10)	23 (11)	0
Weight loss	17 (8)	11 (5)	1 (0.5)
Any adverse event	182 (83)	194 (89)	165 (77)

Tariot et *al*.[63] No. (%) of adverse events occurring at least 5% more with any galantamine than placebo

	Galantamine 8 mg/day (*n* = 140)	Galantamine 16 mg/day (*n* = 279)	Galantamine 24 mg/day (*n* = 273)	Placebo (*n* = 286)
Nausea	8 (5.7)	37 (13.3)	45 (16.5)	13 (4.5)
Vomiting	5 (3.6)	17 (6.1)	27 (9.9)	4 (1.4)
Anorexia	8 (5.7)	18 (6.5)	24 (8.8)	9 (3.1)
Agitation	21 (15.0)	28 (10.0)	22 (8.1)	27 (9.4)
Diarrhoea	7 (5.0)	34 (12.2)	15 (5.5)	17 (5.9)
Any adverse event	106 (75.7)	206 (73.8)	219 (80.2)	206 (72.0)
Any serious adverse event	14 (10.0)	28 (10.0)	35 (12.8)	31 (10.8)
Deaths	1 (0.7)	3 (1.1)	3 (1.1)	4 (1.4)

Wilkinson and Murray[65] No. (%) reported by ≥5% of participants

	Galantamine 18 mg/day (*n* = 88)	Galantamine 24 mg/day (*n* = 56)	Galantamine 36 mg/day (*n* = 54)	Placebo (*n* = 87)
Vomiting	15 (17.0)	4 (7.1)	9 (16.7)	4 (4.6)
Nausea	15 (17.0)	10 (17.9)	20 (37.0)	3.(3.4)
Headache	5 (5.7)	6 (10.7)	8 (14.8)	4 (4.6)
Diarrhoea	2 (2.3)	3 (5.4)	2 (3.7)	2 (2.3)
Decreased appetite	5 (5.7)	2 (3.6)	4 (7.4)	2 (2.3)
Dizziness	4 (4.5)	2 (3.6)	4 (7.4)	3 (3.4)
Any adverse event	49 (55.7)	33 (58.9)	38 (70.4)	38 (43.7)
Any serious adverse event	6 (6.8)	0 (0.0)	5 (9.3)	3 (3.4)

TABLE 32 *Withdrawals due to adverse events for galantamine*

[Commercial/academic confidential information removed]			
Raskind *et al.*[61]			
Galantamine 24 mg/day (*n* = 212)	**Galantamine 32 mg/day (*n* = 211)**		**Placebo (*n* = 213)**
49/212 (23%)	67/211 (32%)		16/213 (8%)
Wilcock *et al.*[64]			
Galantamine 24 mg/day (*n* = 220)	**Galantamine 32 mg/day (*n* = 218)**		**Placebo (*n* = 215)**
31/220 (14%)	48/218 (22%)		19/215 (9%)
Tariot *et al.*[63]			
Galantamine 8 mg/day (*n* = 140)	**Galantamine 16 mg/day (*n* = 279)**	**Galantamine 24 mg/day (*n* = 273)**	**Placebo (*n* = 286)**
9	19	27	20
Wilkinson and Murray[65]			
Galantamine 18 mg/day (*n* = 88)	**Galantamine 24 mg/day (*n* = 56)**	**Galantamine 36 mg/day (*n* = 54)**	**Placebo (*n* = 87)**
19 (21.6%)	10 (17.9%)	24 (44.4%)	8 (9.2%)

were higher among galantamine participants [range: 6% (8 mg/day)–44% (36 mg/day)] than placebo (range 5–9%) (see *Table 32*).

Three trials[61,63,64] demonstrated differential dropout rates between groups for reasons other than adverse events. However, the pattern of the proportion withdrawing was not consistent; in two included trials the dropout rate was greater in the treatment arms but in another study dropout rate was greater in the placebo arm. In three published trials **[commercial/academic confidential information removed]** there appeared to be no difference between groups. No statistical analyses were undertaken by the trials. Very few deaths were reported in any of the included studies. Data relating to withdrawals and deaths for the individual trials can be found in Appendix 9.

Summary

- Six published multicentre placebo-controlled RCTs assessing doses ranging from 8 to 36 mg/day of galantamine over durations of 3–6 months met the inclusion criteria for the systematic review. The methodological quality and the quality of reporting in the studies were variable. Of the six RCTs, three appeared to limit selection bias,[62,64,65] three provided adequate information to reduce the likelihood of measurement bias[61,63,65] and one appeared to guard against the effects of attrition bias.[64] Five RCTs reported that they were sponsored by the manufacturers.
- **[Commercial/academic confidential information removed]**
- Six published RCTs showed that galantamine appears to confer a statistically significant benefit to participants on the ADAS-cog scale when compared with placebo, whether reducing the deterioration or leading to some improvement in their condition. The benefit varies depending on the dose of galantamine. The galantamine–placebo differences in ADAS-cog for 8 mg/day was 1.3 points, 16 mg/day 3.1 points, 18 mg/day 1.7 points, 16 or 24 mg/day 2.5 to 2.8 points, 24–32 mg/day 1.7–3.4 points and 36 mg/day 2.3 points. **[Commercial/academic confidential information removed]** In addition, 14–17% more of galantamine participants were classified as responders (improving by ≥ 4 points on the ADAS-cog) than those on placebo.
- Five published **[commercial/academic confidential information removed]** RCTs assessed the effect of galantamine compared with placebo on the CIBIC-plus, individually showing that higher proportions of participants receiving galantamine experience improvement in their condition compared with those on placebo (0–6.5% more participants). In contrast, a higher proportion of placebo participants tend to deteriorate (4–18% more participants). Also, a higher proportion of galantamine compared with placebo participants were considered to be responders to treatment with differences of between 4% (8 mg/day) and 17%

(24 mg/day). When studies are pooled no statistically significant effects are demonstrated.
- Three RCTs assessed mean changes from baseline on the DAD scale, all reporting statistically significantly slower deterioration for those receiving galantamine 24–32 mg/day compared with placebo. Two RCTs found that participants receiving 16 and/or 24 mg/day galantamine experienced a statistically significantly smaller deterioration on the ADCS/ADL compared with placebo.
- Two published **[commercial/academic confidential information removed]** RCTs found that galantamine had some effect in improving or limiting further deterioration on the NPI scale compared with placebo. Differences in the mean change from baseline were statistically significant for doses of ≥16 mg/day in one of the three studies.
- Adverse events affect participants receiving galantamine more than those on placebo, with between 2 and 27% more participants suffering an adverse event. Nausea, vomiting, dizziness, diarrhoea and anorexia were the main adverse events. Withdrawals due to adverse events resulted in a loss of between 6 and 44% of galantamine participants, with differences following a dose–response relationship.
- The six published **[commercial/academic confidential information removed]** RCTs show benefit for participants receiving galantamine compared with placebo on the outcome measures of ADAS-cog, CIBIC-plus, NPI and DAD, with doses of 16–32 mg/day appearing to be the most effective. Lower doses appear to have limited effect and higher doses have some detrimental effects, particularly in terms of adverse events. Studies were of a short duration and it is difficult to judge the long-term consequences. In addition, it is difficult to assess what the changes on these outcomes mean for people with AD and carers, especially as there are no studies assessing QoL.

Head-to-head drug comparisons

Quantity and quality of research available

Three RCTs met the inclusion criteria for the review. Two compared donepezil with rivastigmine[68,69] and one compared donepezil with galantamine.[70] Details of the study characteristics are given in *Table 33*.

Donepezil versus rivastigmine

Two trials compared donepezil with rivastigmine. Doses of both treatments were different between the two studies. In Fuschillo and colleagues'[68] study, those in the donepezil group were given 5 mg/day and those in the rivastigmine group had 1.5 mg/day for 1 week, increasing weekly in steps of 1.5 mg up to 6–9 mg/day. In Wilkinson and colleagues'[69] study, those in the donepezil arm were given 5 mg/day for 28 days followed by 10 mg/day; those in the rivastigmine arm were initially given 1.5 mg twice daily for 14 days, then 3 mg twice daily for 14 days, then 4.5 mg twice daily for 14 days and finally, if tolerated, were given 6 mg twice daily. Fuschillo and colleagues'[68] study was a single-centre study of just 27 participants. Wilkinson and colleagues'[69] study was a multicentre study (19 centres) with 112 participants. Neither study reported whether sample size calculations was made. The duration of treatment was 30 and 12 weeks in the Fuschillo[68] and Wilkinson[69] studies respectively.

Donepezil versus galantamine

In the trial comparing donepezil with galantamine, those in the donepezil arm were given 5 mg/day for 28 days followed by 10 mg/day; those in the galantamine arm were initially given 4 mg twice daily for 28 days, then 8 mg twice daily for 28 days and then 12 mg twice daily. The RCT was a multicentre study with 120 participants. This study calculated sample sizes and was able to recruit to this number. The duration of treatment was 12 weeks.

Quality assessment

The quality of reporting and methodology of the included RCTs was generally poor by today's standards (see *Table 34*). The method of randomisation was adequate only in the donepezil–galantamine trial[70] and concealment of allocation was inadequate in all trials. These factors increase the risk of selection bias, with the allocation sequence open to possible manipulation. All trials reported adequate eligibility criteria, and all report whether their comparison groups were similar at baseline or not.

As all three trials were open-label RCTs owing to the nature of the comparisons, assessment of blinding of the care provider and patient is classed as not applicable. However, blinding of outcome assessors would be viable, but this was not judged to be adequate in any of the studies. In two studies the outcome assessors were blinded for one outcome; however, this was not the case for the other outcomes reported. These are therefore rated as partial on this criterion. None of the trials included an appropriate ITT analysis.[50] Two of

TABLE 33 *Characteristics of included studies for head-to-head comparisons*

Study	Methods	Participants	Outcomes
Donepezil versus rivastigmine			
Fuschillo *et al.*, 2001[68]	*Design*: RCT *Interventions*: 1. Donepezil 5 mg/day 2. Rivastigmine 1.5 mg/day for 1 week, increasing weekly by steps of 1.5 mg/day to 6–9 mg/day *Number of centres*: 1 *Duration of treatment*: 30 weeks *Sponsor*: not reported	*Inclusion criteria*: AD (DSM-IV and NINCDS-ADRDA); MMSE 10–21 *Numbers*: 27 randomised: 1. 16 to donepezil 5 mg/day 2. 11 to rivastigmine 1.5–9 mg/day *Mean age ± SD (range)*: 1. 68.1 ± 5.6 (54–77) 2. 66.2 ± 9.2 (53–77)	*Primary outcomes*: • MMSE • ADAS-cog • Physical Self Maintenance Scale (PSMS) of the ADL test *Secondary outcomes*: • Adverse events
Wilkinson *et al.*, 2002[69]	*Design*: RCT, multicentre *Interventions*: 1. Donepezil 5 mg/day for 28 days then 10 mg/day 2. Rivastigmine 1.5 mg b.d., increasing to 3 mg b.d. (day 14), 4.5 mg b.d. (day 28) and finally 6 mg b.d. (day 42) if tolerated *Number of centres*: 19 *Duration of treatment*: 12 weeks *Sponsor*: Eisai and Pfizer	*Inclusion criteria*: ≥ 50 years old; mild to moderate, possible or probable AD (DSM-IV and NINCDS-ADRDA); MMSE 10–26 *Numbers*: 112 participants randomised: 1. 57[a] to donepezil 5 mg/day 2. 55 to rivastigmine 3–12 mg/day *Mean age ± SD (range)*: 1. 74.0 ± 7.6 (51–87) 2. 74.9 ± 7.3 (52–90) [a] 1 patient in the donepezil group did not receive any study medication.	*Primary outcomes*: • ADAS-cog (11-item version) • MMSE *Secondary outcomes*: • Adverse events
Donepezil versus galantamine			
Jones *et al.*, 2004[70]	*Design*: RCT, multicentre *Interventions*: 1. Donepezil 5 mg/day for 4 weeks, then 10 mg/day 2. Galantamine 4 mg b.d. for 4 weeks, 8 mg b.d. for a further 4 weeks, then 12 mg b.d. *Number of centres*: 14 *Duration of treatment*: 12 weeks *Sponsor*: Eisai and Pfizer Pharmaceuticals	*Inclusion criteria*: ≥ 50 years of age; probable or possible, mild or moderate AD (DSM-IV and NINCDS-ADRDA); MMSE 10–24 *Numbers*: 120 randomised: 1. 64 to donepezil 2. 56 to galantamine *Mean age ± SD (range)*: 1. 73.8 ± 7.4 (51–88) 2. 75.1 ± 7.7 (53–89)	*Primary outcomes*: • Physician's and Caregiver's Satisfaction Questionnaires (P&CSQ) *Secondary outcomes*: • ADAS-cog (11-item and 13-item versions) • MMSE • DAD • Adverse events

TABLE 34 *Quality assessment table for head-to-head comparisons*

Study	Randomisation	Concealment of allocation	Baseline characteristics	Eligibility	Blinding of assessors	Care provider blinding	Patient blinding	Reporting outcomes	ITT analysis	Withdrawals explained
Donepezil versus rivastigmine										
Fuschillo *et al.*[68]	Un	Un	Rep	Ad	In	NA	NA	Ad	In	Un
Wilkinson *et al.*[69]	Un	Un	Rep	Ad	Par	NA	NA	Ad	In	Ad
Donepezil versus galantamine										
Jones *et al.*[70]	Ad	Un	Rep	Ad	Par	NA	NA	In	In	Ad

Ad, adequate; In, inadequate; Par, partial; Rep, reported; Un, unknown; NA, not applicable.

TABLE 35 *ADAS-cog for donepezil versus rivastigmine*

Fuschillo et *al.*[68] Mean ± SD score		
Donepezil 5 mg/day (*n* = 16)	**Rivastigmine 1.5–9 mg/day (*n* = 11)**	**Treatment difference between groups**
39.4 ± 6.6 (baseline 43.0 ± 7.6)	36.5 ± 5.7 (baseline 40.3 ± 6.7)	Not reported
Wilkinson et *al.*[69] Mean ± SEM change from baseline		
Donepezil 5 mg/day (*n* = 50)	**Rivastigmine 3–12 mg/day (*n* = 37)**	**Treatment difference between groups (95% CI)**
–0.90 ± 0.56	–1.05 ± 0.67	–0.15 (–1.85 to 1.55)

TABLE 36 *MMSE for donepezil versus rivastigmine*

Fuschillo et *al.*[68] Mean ± SD score		
Donepezil 5 mg/day (*n* = 16)	**Rivastigmine 1.5–9 mg/day (*n* = 11)**	**Treatment difference between groups**
14.9 ± 4.4 (baseline 13.7 ± 3.4)	16.0 ± 3.6 (baseline 13.2 ± 3.3)	Not reported
Wilkinson et *al.*[69] Mean ± SEM change from baseline		
Donepezil 5 mg/day (*n* = 51)	**Rivastigmine 3–12 mg/day (*n* = 39)**	**Treatment difference between groups (95% CI)**
0.71 ± 0.44	1.20 ± 0.52	0.49 (–0.82 to 1.81)

the included studies[69,70] state that an ITT analysis was undertaken; however, the methods used do not meet the definition of ITT and therefore these studies are categorised as inadequate on this quality criterion. Two studies give details of the numbers of and reasons for withdrawals from the study.[69,70]

Assessment of effectiveness: donepezil versus rivastigmine

Cognitive outcomes

ADAS-cog

Both RCTs report the ADAS-cog and the results are given in *Table 35*. The study by Fuschillo and colleagues[68] reported the mean ADAS-cog score at endpoint, whereas that by Wilkinson and colleagues[69] reported the mean change from baseline. To aid interpretation, the baseline ADAS-cog for the Fuschillo and colleagues study has been added to *Table 35* (in parentheses).

On the ADAS-cog a negative mean change indicates a clinical improvement. Both included studies show comparable improvements on the ADAS-cog in the donepezil-treated and the rivastigmine-treated participants, but statistical comparisons are not reported for either study.

MMSE

Both RCTs report the MMSE and results are given in *Table 36*. The Fuschillo and colleagues[68] study reported the mean MMSE score at endpoint, whereas the Wilkinson and colleagues[69] study reported the mean change from baseline. To aid interpretation, the baseline MMSE score for the Fuschillo and colleagues study has been added to *Table 36* (in parentheses).

On the MMSE a positive mean change indicates a clinical improvement. Both included studies show improvements on the MMSE in the donepezil-treated and the rivastigmine-treated participants. In both studies the difference from baseline in the rivastigmine groups can be observed to be greater than that of the donepezil group, but statistical comparisons are not reported for either study.

Functional outcomes

PSMS

The Physical Self-Maintenance Scale (PSMS) was used in one included trial.[68] On this scale, which measures ADLs, a decreased change in score indicates improvement. At 30 weeks the mean PSMS in the donepezil-treated group was 9.1 (baseline 9.2) and in the rivastigmine-treated

TABLE 37 *Adverse events for donepezil versus rivastigmine*

Fuschillo et *al.*[68] % occurrence		
	Donepezil 5 mg/day (*n* = 16)	**Rivastigmine 1.5–9 mg/day (*n* = 11)**
Nausea	8	15
Vomiting	5	10
Dizziness	10	15
Diarrhoea	8	10
Abdominal pain	5	8
Headache	8	10
Wilkinson et *al.*[69] Treatment-emergent AEs occurring in ≥5% of participants and more than twice as frequently in either treatment group (all causalities). No. (%)		
	Donepezil 5 mg/day (*n* = 56)	**Rivastigmine 3–12 mg/day (*n* = 55)**
Nausea	6 (10.7)	23 (41.8)
Vomiting	4 (7.1)	13 (23.6)
Headache	4 (7.1)	10 (18.2)
Anorexia	1 (1.8)	5 (9.1)
Abnormal dreams	4 (7.1)	1 (1.8)
Back pain	4 (7.1)	0
Somnolence	1 (1.8)	3 (5.5)
Urinary tract infection	3 (5.4)	0
Proportion experiencing ≥ 1 treatment-related advance event	42.9%	58.2%

group 11.0 (baseline 11.5). Statistical analyses were within-group rather than between-group comparisons.

Compliance

Wilkinson and colleagues[69] assessed compliance between those given donepezil and those given rivastigmine. Those defined as reaching the maximum daily dose at some time during the study were 98.2% in the donepezil group and 60% in the rivastigmine group. Those defined as remaining at the maximum dose until study completion or the final visit were 87.5% in the donepezil group and 47.3% in the rivastigmine group. These differences were not tested for statistical significance.

Adverse events

Various event rates for selected adverse events were reported in the included trials and can be seen in *Table 37*. The most commonly reported adverse events related to the gastrointestinal system, including nausea, vomiting and diarrhoea. Rates of adverse events were generally higher in the rivastigmine-treated participants than in the donepezil-treated participants, but no statistical comparisons between the treatment groups were reported. Adverse events were generally mild to moderate in severity; however, four participants in the rivastigmine group of the Wilkinson and colleagues[69] study reported a severe treatment-related digestive system adverse event compared with none in the donepezil group. Fuschillo and colleagues[68] reported no withdrawals due to adverse events in either study group. In the Wilkinson and colleagues[69] study 10.7% of donepezil-treated participants and 21.8% of rivastigmine-treated participants withdrew owing to the onset of adverse events. Withdrawals unrelated to adverse events were reported in the Wilkinson and colleagues[69] study, where more patients withdrew or died in the rivastigmine group than the donepezil group, but this was not tested for statistical significance. Data relating to withdrawals are given in Appendix 10.

Summary

- Two studies compared treatment with donepezil with treatment with rivastigmine. The methodological quality and the quality of reporting in the studies was generally poor and one study had a small sample size. One study was funded by the manufacturers of donepezil.
- On measures of cognitive ability, general trends suggest that treatment with rivastigmine (1.5–12 mg/day) leads to more improvement than treatment with 5 mg/day donepezil; however, these trends are small, are not tested for statistical significance and may also reflect the differences in the doses given.

- One RCT noted similar rates of improvement on ADLs; in each comparison arm the improvement was noted to be small.
- Rates of adverse events tended to be higher in those participants in the rivastigmine groups than the donepezil groups and more participants withdrew owing to adverse events in the rivastigmine groups. The effects of the doses reported may reflect on these differences.

Assessment of effectiveness: donepezil versus galantamine

Cognitive outcomes

ADAS-cog

The one included trial[70] reported data on the ADAS-cog, and results are given in Appendix 10. On the ADAS-cog a negative mean change indicates a clinical improvement. At 12 weeks the mean change from baseline was shown to be statistically significantly lower (better) in the donepezil group compared with the galantamine group (–4.7 donepezil, –2.3 galantamine, $p < 0.01$).

Cognitive responders on ADAS-cog. This included study[70] also reported data on 'cognitive responders'. Good cognitive responders were defined as those with at least a 4-point improvement on the ADAS-cog; they also present data on those with 'substantial' response with at least a 7-point improvement. In this study 53.3% of participants given donepezil and 28.8% of participants given galantamine had at least a 4-point improvement. This difference was statistically significant ($p = 0.009$). Participants with at least a 7-point improvement on ADAS-cog were 28.3% in the donepezil group and 11.5% in the galantamine group. The difference between the study groups was also shown to be statistically significant ($p = 0.029$).

MMSE

On the MMSE, a positive mean change indicates a clinical improvement. The included trial comparing donepezil with galantamine demonstrated a statistically significant difference in the improvement on the MMSE between study groups. The MMSE at week 12 was 1.6 in the donepezil group and 0.8 in the galantamine group ($p < 0.05$).

Functional outcomes

DAD

The DAD scale was used to assess function in this one included trial. On the DAD a positive score indicates clinical improvement. This study demonstrated a positive mean change of 1.5 from baseline at 12 weeks in the donepezil group and a mean change of –0.4 point in the galantamine group. The difference between these groups was shown to be statistically significant ($p < 0.05$).

Compliance

Jones and colleagues[70] assessed compliance between those given donepezil and those given galantamine. Those defined as reaching the maximum daily dose at some time during the study were 98.4% in the donepezil group and 94.6% in the galantamine group. Those defined as remaining at the maximum dose until study completion or the final visit were 92.2% in the donepezil group and 71.4% in the galantamine group. These proportions were not compared statistically.

Adverse events

Rates of treatment-emergent adverse events reported in the Jones and colleagues[70] study were generally higher in the galantamine-treated participants than in the donepezil-treated participants. Most adverse events related to the gastrointestinal system: rates of nausea, vomiting and diarrhoea were 15.6, 0 and 9.4% in the donepezil groups, respectively, and 23.2, 12.5 and 14.3% in the galantamine groups, respectively. Serious adverse events were experienced by 6.3% of participants in the donepezil group compared with 3.6% in the galantamine group. Three participants (4.7%) treated with donepezil withdrew from the study owing to adverse events compared with four participants (7.1%) treated with galantamine.

Summary

- One RCT was included that compared donepezil treatment with galantamine treatment. The methodological quality and the quality of reporting in this study were generally poor and this study was funded by the manufacturers of donepezil. The study was of a short duration, and the dose titration regimen of galantamine meant that participants were on the high dose for half as long as those in the donepezil group.
- Participants treated with either drug demonstrated improvements on the ADAS-cog scale; however, treatment with donepezil conferred a statistically significant benefit to participants on the scale when compared with treatment with galantamine.
- ADLs as measured by the DAD scale were shown to be statistically significantly improved in the donepezil group compared with the galantamine group.

- Rates of mild to moderate adverse events were shown to be higher in the galantamine group compared with the donepezil group; however, rates of serious adverse events appeared to be higher in the donepezil group. Higher proportions of participants withdrew owing to adverse events in the galantamine group than the donepezil group.

Memantine

Quantity and quality of research

Two RCTs met the inclusion criteria for the review. Details of the study characteristics are summarised in *Table 38* with further details in Appendix 11. Both studies report data on participants with moderately severe to severe AD, as measured by the MMSE, although the range on the MMSE score varies slightly between them, as can be seen in *Table 38*.

Both studies compared one dose of memantine (20 mg/day) versus placebo. In one study[71] treatment was titrated in 5-mg weekly increments from a starting dose of 5 mg/day to the target of 20 mg/day at the beginning of week 4. All participants receiving memantine were required to receive the target dose of 20 mg/day by the end of week 8, or else they were disenrolled. Both trials were multicentred with sample size ranging from 252[72] to 404.[71] The sample size required was calculated in just one of the studies.[71] The duration of treatment was 24 weeks in one study[71] and 28 weeks in the other.[72] One major difference exists between the two studies regarding drug treatments. The participants in the study by Tariot and colleagues[71] were included on the basis that they had already been receiving donepezil for more than 6 months before entrance into the trial and at a stable dose (5–10 mg/day) for at least 3 months. These participants maintained stable donepezil therapy at the entry dose as prescribed

TABLE 38 *Characteristics of included studies for memantine*

Study	Methods	Participants	Outcomes
Reisberg *et al.*, 2003[72]	*Design*: RCT, multicentre, placebo controlled, double-blind, parallel group *Interventions*: 1. Memantine 20 mg/day 2. Placebo *Number of centres*: 32 *Duration of treatment*: 28 weeks (mean ± SD duration of treatment for both groups 24 ± 8 weeks) *Sponsor*: Merz Pharmaceuticals (Frankfurt, Germany) and National Institute on Aging of the National Institutes of Health	*Inclusion criteria*: ≥ 50 years old; probable AD (DSM-IV and NINCDS-ADRDA); MMSE 3–14, GDS stage 5 or 6, FAST stage ≥ 6a *Numbers*: 252 randomised: 1. 126 to memantine 20 mg/day 2. 126 to placebo *Mean age*: 76.1 ± 8.07	*Primary outcomes*: • CIBIC-plus • ADCS/ADLsev *Secondary outcomes*: • SIB • MMSE • GDS • FAST • NPI • Resource Utilisation in Dementia instrument • Adverse events
Tariot *et al.*, 2004[71]	*Design*: RCT, multicentre, placebo controlled, double-blind *Interventions*: 1. Memantine 20 mg/day 2. Placebo *Number of centres*: 37 *Duration of treatment*: 24 weeks *Sponsor*: Forest Research Institute (a division of Forest Laboratories)	*Inclusion criteria*: probable AD (NINCDS-ADRDA); MMSE 5–14; ≥ 50 years; ongoing cholinesterase inhibitor therapy with donepezil 6 months before study entrance and at steady dose (5–10 mg/day) for at least 3 months *Numbers*: 404 randomised: 1. 203 to memantine 20 mg/day (reduced to 202 as 1 withdrew consent before receiving treatment) 2. 201 to placebo *Mean age*: 1. 75.5 (8.45) 2. 75.5 (8.73)	*Primary outcomes*: • SIB • ADCS/ADL *Secondary outcomes*: • CIBIC-plus • NPI • BGP • Adverse effects

by the patient's physician for the duration of the study. Participants from the study by Reisberg and colleagues[72] were not receiving any ongoing cholinesterase inhibitor therapy.

The main primary outcome measure used in the two studies is the ADCS/ADLsev. Other outcomes common to both studies are the CIBIC-plus, the SIB and the NPI. The Reisberg study also used the MMSE, the GDS and the Functioning Assessment Staging Scale (FAST). Tariot and colleagues also included the Behavioural Rating Scale for Geriatric Patients (BGP). Adverse events were also recorded in both studies.

The quality of reporting and methodology of the two included RCTs was generally good (see *Table 39*). The method of randomisation was adequate in both studies, as was the concealment of allocation. Likewise, both studies reported on whether or not the comparison groups were similar at baseline, and also reported eligibility criteria. These factors should limit the possibility of selection bias. Blinding was adequate in both studies with regard to the assessors, the care provider and the patient, therefore reducing the risk of measurement bias. In both cases, the drug and placebo tablets were described as being identical. The studies adequately reported the point estimates and measures of variability for the primary outcomes. However, although the studies reported that they undertook an ITT analysis, neither study was rated as demonstrating an adequate ITT. One study, for example, defined the ITT as participants in the safety population who completed at least one postbaseline efficacy assessment.[71] Both studies did, however, adequately explain any patient withdrawals.

Assessment of clinical effectiveness

Functional outcome measurements

ADCS/ADL

The primary outcome used in both studies was the ADCS/ADLsev (also known as ADCS/ADL$_{19}$). This is a 19-item subset of the original 42-item inventory focusing on items appropriate for the assessment of the later stages of dementia. Results are given in *Table 40*. It has a range of possible scores from 0 to 54, with a higher score indicating a better function.

Both trials reported statistically significant improvements. In the study by Reisberg and colleagues,[72] the total ADCS/ADLsev scores at baseline were similar in the two groups (26.8 in the memantine group and 27.4 in the placebo group). The mean change from baseline was –3.1 in the memantine group and –5.2 in the placebo

TABLE 39 *Quality assessment table for memantine*

Study	Randomisation	Concealment of allocation	Baseline characteristics	Eligibility	Blinding of assessors	Care provider blinding	Patient blinding	Reporting outcomes	ITT analysis	Withdrawals explained
Reisberg *et al.*[72]	Ad	Un	Rep	Ad	Par	Ad	Ad	Ad	In	Ad
Tariot *et al.*[71]	Ad	Ad	Rep	Ad	Un	Ad	Ad	Ad	In	Ad

Ad, adequate; In, inadequate; Par, partial; Rep, reported; Un, unknown.

TABLE 40 *ADCS/ADL for memantine*

Reisberg *et al.*[72] ADCS/ADLsev: mean (± SD) change from baseline		
Memantine 20 mg/day (*n* = 124)	**Placebo (*n* = 123)**	***p*-Value vs placebo**
–3.1 ± 6.79	–5.2 ± 6.33	0.02
Tariot *et al.*[71] ADCS/ADL$_{19}$: least-squares mean score (SE) change from baseline		
Memantine 20 mg/day (*n* = 198)	**Placebo (*n* = 197)**	***p*-Value vs placebo**
–2.0 (0.50)	–3.4 (0.51)	0.03

TABLE 41 *CIBIC-plus for memantine*

Reisberg et *al.*[72] Mean ± SD (*n*) change from baseline		
Memantine 20 mg/day (*n* = 118)	**Placebo (*n* = 118)**	***p*-Value vs placebo**
4.5 ± 1.12	4.8 ± 1.09	0.06
Tariot et *al.*[71] Mean (SE) change from baseline		
Memantine 20 mg/day (*n* = 198)	**Placebo (*n* = 196)**	***p*-Value vs placebo**
4.41 (0.074)	4.66 (0.075)	0.03
Distribution (% of participants) of CIBIC-plus ratings at endpoint		
Memantine 20 mg/day (*n* = 198)	**Placebo (*n* = 196)**	***p*-Value vs placebo**
1 = marked improvement 1% 2 = moderate improvement 4% 3 = minimal improvement 8% 4 = no change 4% 5 = minimal worsening 31% 6 = moderate worsening 14% 7 = marked worsening 1%	1 = marked improvement 0% 2 = moderate improvement 2% 3 = minimal improvement 10% 4 = no change 33% 5 = minimal worsening 32% 6 = moderate worsening 20% 7 = marked worsening 3%	$p = 0.03$ for the comparison between the distribution of values for the memantine and placebo groups

group. At the endpoint, there was statistically significantly less deterioration in the memantine group than in the placebo group.

In the study by Tariot and colleagues,[71] analyses using the LOCF approach showed a statistically significant benefit of memantine versus treatment with placebo. The mean change from baseline was –2.0 for the memantine group and –3.4 in the placebo group.

Both studies, therefore, showed less deterioration in the memantine group than the placebo group, although this was more evident in the Tariot and colleagues study.[71] This variation may be explained by the combined use of donepezil and memantine by participants in this study.[71]

Summary: less deterioration in functional outcome was apparent in the memantine group compared with placebo as measured by the ADCS/ADL.

Global outcomes

CIBIC-plus

Both studies report the CIBIC-plus as a test for global outcomes and can be seen in *Table 41*. One reported it as a primary outcome[72] and the other as a secondary outcome.[71] The CIBIC-plus uses a seven-point Likert-type scale ranging from 1 (= marked improvement) to 7 (= marked worsening).

The mean change from baseline ranged from 4.41[71] to 4.5[72] in the memantine groups and from 4.66[71] to 4.8[72] in the placebo group. Scores therefore were similar and the two studies reported statistically significant improvement in global measures using CIBIC-plus. In the study by Reisberg and colleagues, the CIBIC-ratings at the endpoint (mean difference between the groups 0.3l; $p = 0.06$) supported the effectiveness of memantine.

The study by Tariot and colleagues[71] showed that the mean CIBIC-plus score was statistically significantly better for the memantine group versus the placebo group using LOCF. Furthermore, 55% of the memantine group was rated as improved or unchanged versus 45% of the placebo group at endpoint.

Summary: memantine appears to be more effective than placebo in improving global function using the CIBIC-plus.

Cognitive outcomes

SIB

The SIB is a test developed for the evaluation of cognitive dysfunction in participants with more severe AD. It assesses social interaction, memory, language, visuo-spatial ability, attention, praxis and construction. The SIB scores range from 0 to 100, with higher scores reflecting higher levels of cognitive ability. Both studies report data using the SIB, with one using it as a primary outcome[71] and the other as a secondary outcome.[72] Results are shown in *Table 42*.

Statistically significant improvements were reported in the SIB. The mean change from baseline scores ranged from –4.0 to 0.9 in the memantine groups and between –10.1 and –2.5 in the placebo groups. In the Reisberg and colleagues study,[72] the SIB showed statistically significant differences favouring

TABLE 42 *Severe Impairment Battery for memantine*

Reisberg *et al.*[72] Mean ± SD change from baseline		
Memantine 20 mg/day (*n* = 124)	**Placebo (*n* = 123)**	***p*-Value vs placebo**
–4.0 ± 11.34	–10.1 ± 13.50	$p < 0.001$
Tariot *et al.*[71] Least-squares mean score (SE) change from baseline		
Memantine 20 mg/day (*n* = 198)	**Placebo (*n* = 196)**	***p*-Value vs placebo**
0.9 (0.67)	–2.5 (0.69)	$p < 0.001$

TABLE 43 *MMSE for memantine*

Reisberg *et al.*[72] MMSE mean ± SD change from baseline		
Memantine 20 mg/day (*n* = 124)	**Placebo (*n* = 124)**	***p*-Value vs placebo**
–0.5 ± 2.40	–1.2 ± 3.02	NS

TABLE 44 *NPI for memantine*

Reisberg *et al.*[72] Mean ± SD change from baseline		
Memantine 20 mg/day (*n* = 120)	**Placebo (*n* = 119)**	***p*-Value vs placebo**
0.5 ± 15.76	3.8 ± 16.06	$p = 0.33$ (ns)
Tariot *et al.*[71] Least-squares mean score (SE) change from baseline		
Memantine 20 mg/day (*n* = 193)	**Placebo (*n* = 189)**	***p*-Value vs placebo**
–0.1 (0.98)	3.7 (0.99)	$p = 0.002$

memantine. On the basis of the predetermined definition of a response in the study protocol, 29% of the participants receiving memantine and 10% of those receiving placebo had a response. In the Tariot and colleagues study,[71] analyses using the LOCF approach also showed a statistically significant benefit of memantine versus treatment with placebo. *Table 42* shows that there was less deterioration (and a slight improvement in the memantine group) in SIB scores in the Tariot and colleagues study[71] (where participants on memantine were already on a steady dose of donepezil) than in the Reisberg and colleagues study (where participants were on memantine only).

Summary: less deterioration of cognitive function was apparent in the memantine group than in placebo. This was even more apparent in those participants from the study by Tariot and colleagues, who were also on a steady dose of donepezil.

MMSE

Both studies reported a mean MMSE score at baseline. Reisberg and colleagues[72] reported a mean ± SD score of 7.8 ± 3.76 in the memantine group and 8.1 ± 3.60 in the placebo group. Tariot and colleagues[71] reported memantine and placebo group mean MMSE scores (SD) as 9.9 (3.13) and 10.2 (2.98), respectively, indicating that they had better function at baseline than participants in the other memantine study. However, only one study reported the MMSE change from baseline at endpoint[72] and the results are given in *Table 43*. A positive mean change on the MMSE indicates a clinical improvement.

As can be seen from the table, neither group showed an improvement in MMSE score and although there was less deterioration in the memantine group, there was no statistically significant difference between the two.

Summary: MMSE scores deteriorated in both the memantine group and the placebo group and the degree of deterioration was not statistically significantly different between the two groups.

Behaviour and mood

NPI

The two studies reported results using the NPI as shown in *Table 44*. The NPI assesses

TABLE 45 *Additional outcome measures for memantine*

Reisberg et *al.*[72]		
Memantine 20 mg/day	**Placebo**	***p*-Value vs placebo**
GDS: mean ± SD change from baseline		
n = 121 0.1 ± 0.47	*n* = 119 0.2 ± 0.48	*p* = 0.11 (ns)
FAST: mean ± SD change from baseline		
n = 121 –0.2 ± 1.24	*n* = 118 0.6 ± 1.39	*p* = 0.02
Tariot et *al.*[71]		
Memantine 20 mg/day	**Placebo**	***p*-Value vs placebo**
BGP: least-squares mean (SE) changes from baseline		
n = 185 0.8 (0.37)	*n* = 179 2.3 (0.38)	*p* = 0.001

neuropsychiatric disturbances with a 12-item scale based on information from the caregiver. The total score ranges from 0 to 144 with higher scores reflecting greater symptoms.

As shown in the table, the change from baseline at endpoint ranged from –0.1 to 0.5 in the memantine groups and from 3.7 to 3.8 in the placebo groups. In one study[71] the total NPI score was statistically significantly lower for the memantine group compared with the placebo group at week 24, representing fewer behavioural disturbances and psychiatric symptoms for participants in the memantine group. In the other study, however,[72] no statistically significant differences were observed between treatment groups. It appears, therefore, that memantine is more effective in participants with moderately severe to severe AD already receiving donepezil, as measured by the NPI.

Summary: it appears that participants receiving memantine and already receiving a steady dose of donepezil have a statistically significantly lower NPI score than placebo. Those on memantine only, however, showed no statistically significant difference compared with placebo.

Other outcome measures

A few additional secondary outcome measures were used in either one or the other of the memantine studies. These are described and shown in *Table 45*.

Global Deterioration Scale. The GDS was used as a secondary outcome in one study.[72] It is a seven-stage scale, with higher stages signifying greater impairment. Baseline scores were 5.5 (memantine group, $n = 126$) and 5.6 (placebo group, $n = 126$). As with the MMSE score and the NPI, no statistically significant differences were observed between treatment groups in the GDS.[72]

Functional Assessment Staging Score. The FAST scale assesses the magnitude of progressive functional deterioration in participants with dementia by identifying characteristic progressive disabilities. Its seven major stages range from normal (stage 1) to severe dementia (stage 7). Reisberg and colleagues[72] reported that memantine-treated participants showed statistically significantly less deterioration in their functional AD stage, as measured by the FAST, than those placebo-treated participants.

Behavioural Rating Scale for Geriatric Patients. The BGP was reported in one study,[71] and was administered at baseline and final visit only. It consists of 35 items (scored 0, 1 or 2) assessing observable aspects of cognition, function and behaviour. A higher score reflects worse function. The BGP care dependency subscale reflects cognitive and functional characteristics associated with increased need for care.

Table 45 shows that the BGP care dependency subscale was statistically significantly improved for the memantine group compared with the placebo group.

Reisberg and colleagues[72] showed no statistically significant difference between the memantine and placebo groups as measured by the MMSE, the GDS stage or NPI score. A subgroup analysis examined whether efficacy was seen in both participants with moderate AD (MMSE score

TABLE 46 *Adverse events for memantine*

Reisberg *et al.*[72] Adverse events: No. (%)			
Adverse event	**Memantine 20 mg/day (*n* = 126)**	**Placebo (*n* = 126)**	***p*-Value vs placebo**
Any adverse event	106 (84)	109 (87)	Not reported
Agitation	23 (18)	40 (32)	Not reported
Urinary incontinence	14 (11)	14 (11)	Not reported
Urinary tract infection	7 (6)	17 (13)	Not reported
Insomnia	13 (10)	10 (8)	Not reported
Diarrhoea	12 (10)	10 (8)	Not reported
Tariot *et al.*[71] Adverse events: No. (%)			
Adverse event	**Memantine 20 mg/day (*n* = 202)**	**Placebo (*n* = 201)**	***p*-Value vs placebo**
Adverse events reported in at least 5% of participants in either group	78%	72%	
Agitation	19 (9.4)	24 (11.9)	Not reported
Confusion	16 (7.9)	4 (2.0)	$p = 0.1$
Fall	15 (7.4)	14 (7.0)	Not reported
Influenza-like symptoms	15 (7.4)	13 (6.5)	Not reported
Dizziness	14 (6.9)	16 (8.0)	Not reported
Headache	13 (6.4)	5 (2.5)	$p = 0.9$
Urinary tract infection	12 (5.9)	10 (5.0)	Not reported
Urinary incontinence	11 (5.4)	6 (3.0)	Not reported
Accidental injury	10 (5.0)	16 (8.0)	Not reported
Upper respiratory tract infection	10 (5.0)	13 (6.5)	Not reported
Peripheral edema	10 (5.0)	8 (4.0)	Not reported
Diarrhoea	9 (4.5)	17 (8.5)	Not reported
Faecal incontinence	4 (2.0)	10 (5.0)	Not reported

TABLE 47 *Withdrawals due to adverse events for memantine*

Reisberg *et al.*[72] Withdrawals due to adverse events: No. (%)	13 (10)	22 (17)
Tariot *et al.*[71] Withdrawals due to adverse events: No (%)	15 (7.4)	25 (12.4)

10–14) and those with severe AD (MMSE score >10). A benefit of memantine compared with placebo was suggested for all outcome measures in both groups. The required caregiver time, as assessed by the Resource Utilization in Dementia score, was analysed. The result was statistically significant, indicating that caregivers spent less time with participants receiving memantine (difference between treatment groups, 45.8 hours per month; 95% CI: 10.37 to 81.27; $p = 0.01$).

Adverse events

Adverse events were reported in both studies. These are shown in *Table 46*. The number of participants withdrawing owing to adverse events is shown in *Table 47*.

The majority of participants in the Reisberg and colleagues study[72] experienced adverse events (84% with memantine and 87% with placebo). Most adverse events were mild to moderate in severity and were either not related or unlikely to be related to the study medication. The incidence rates for the frequently reported adverse events in the memantine group were no more than 2% higher than in the placebo group. Serious adverse events were reported in 16 (13%) of participants receiving memantine and 23 (18%) of participants receiving placebo. Most of the serious adverse events were considered to be unrelated to study medication. More participants receiving placebo than participants receiving memantine discontinued the study prematurely owing to adverse events.

As can be seen from the *Table 46*, adverse events occurred in 78% of the memantine and 72% of the placebo groups in the Tariot and colleagues

study.[71] Most adverse events were rated as mild or moderate in severity and were judged not to be related to the study drug for participants in both treatment groups. The only adverse events that occurred in at least 5% of the memantine group and with an incidence of at least twice that of the placebo group were confusion and headache. By similar criteria, lower incidences of diarrhoea and faecal incontinence were observed in the memantine group compared with the placebo group. Other gastrointestinal effects of interest for participants receiving cholinesterase inhibitors included nausea (memantine group 0.5%; placebo group 3.5%) and constipation (memantine group 3.0%; placebo group 1.5%). Four (25%) of 16 participants experiencing confusion discontinued because of this adverse event compared with three (75%) of four participants receiving placebo who experienced this adverse event. In most of the participants receiving memantine, confusion was rated as mild, occurred at a median of 32 days and remitted within 2 weeks. In participants receiving placebo, confusion was more likely to be rated as severe, occurred at a median of 55 days and did not remit. No participants discontinued because of headache, which usually lasted 1 day.

Withdrawals due to adverse events

Both studies reported withdrawals related to adverse events and these are shown in *Table 47*. As can be seen from the results, there was not a very large variation in the number of people who withdrew between the two studies. Withdrawals due to adverse events ranged from 7.4 to 10% in the memantine group and from 12.4 to 17% in the placebo group. *p*-Values were not reported for either study.

Withdrawals unrelated to adverse events were shown to be similar between groups in one included study,[72] and higher in the placebo group in the other study.[71] No statistical comparisons were made in either trial. Deaths were reported to be slightly higher in the placebo group in one study,[72] but again this was not tested for statistical significance. Data relating to withdrawals can be found in Appendix 11.

Summary

- Two multicentre placebo controlled RCTs assessing doses of 20 mg/day of memantine over durations of 24–28 weeks met the inclusion criteria for the systematic review. Participants included were those with moderately severe to severe AD. The methodological quality and the quality of reporting in the studies were generally of a good standard.
- Both RCTs investigating the use of memantine versus placebo showed some statistically significant improvements in outcomes for memantine compared with placebo. Both studies demonstrated that memantine appears to show a statistically significant benefit to participants on the ADCS/ADL when compared with placebo, with a reduction in the level of deterioration. Likewise, both studies used the CIBIC-plus as a measure of global outcome and, in both cases, memantine appeared to be effective.
- Both studies used the SIB as a measure of cognitive outcome. Statistically significant differences in favour of the use of memantine over placebo were apparent in the two studies, although a greater effect was shown in the study by Tariot and colleagues,[71] where an increase (0.9) in CIBIC-plus score occurred, rather than the study by Reisberg and colleagues,[72] where a deterioration in score occurred (–4.0).
- The two studies are not able to be combined in a meta-analysis owing to heterogeneity between the two patient groups, that is, participants already receiving donepezil versus participants not already receiving a cholinesterase inhibitor. The reporting of similar outcome measures in the two studies, such as the ADCS/ADL and the CIBIC-plus, tend to suggest, however, that a more favourable effect is apparent in the study by Tariot and colleagues.[71] It could be suggested, therefore, that memantine is more effective in participants who are already receiving donepezil and continue to do so. However, there are no other RCTs of this kind to compare with and therefore this statement cannot be made with any degree of conviction. It must also be pointed out that the study sample was larger ($n = 404$) than that in the study by Reisberg and colleagues[72] ($n = 252$).
- The frequency of adverse events was similar for both the memantine and placebo groups. In the Reisberg and colleagues[72] study, the incidence rates for frequently reported adverse events in the memantine group were no more than 2% higher than in the placebo group. Likewise, in the study by Tariot and colleagues,[71] the percentage of participants experiencing adverse events in the memantine and placebo groups was 78 and 72%, respectively. Withdrawals due to adverse events resulted in a loss of between 7.4 and 10% of memantine participants.
- The two RCTs show benefit for participants receiving memantine compared with placebo on the outcome measures of ADCS/ADL, CIBIC-plus and SIB, appearing to be most effective in participants already receiving a steady dose of

donepezil. Studies were of a short duration and it is therefore difficult to judge the long-term consequences. Furthermore, it is difficult to assess what the changes on these outcomes mean for people with AD and their carers, especially as there are no studies assessing QoL.

Chapter 5

Evidence from systematic reviews

A number of systematic reviews of the cholinesterase inhibitors and memantine for AD were identified. In addition, literature reviews that did not use systematic methods were located but these will not be discussed further. Some of the systematic reviews identified did not use the same inclusion criteria as those set out for the current review. In particular, most did not impose any requirement for the severity of AD in the population. Some reviews, however, did share the same inclusion criteria of the current review and brief summaries are provided below. No formal data extraction or quality assessment of these systematic reviews was undertaken.

Donepezil

Two systematic reviews met the inclusion criteria.

Wolfson and colleagues[74]

This review did not include mild to moderate severity as an inclusion criterion. However, all studies reviewed included participants with mild to moderately severe AD and so it is presented here. This review also reports data for a number of other drugs including rivastigmine (see below), metrifonate and Ginkgo Biloba; however, the last two do not meet the inclusion criteria of the present review and are not discussed here. A subsequent publication based on this included review includes an updated search and includes an additional four donepezil studies. This publication, however, includes a trial that does not meet the inclusion criteria for the current review for this drug.

Four studies were included in the review for donepezil, all of which are included in the present review. A summary of results is given here to provide a comparison for the results of the present review. The review reports that overall the trials are consistent in the finding that donepezil is a well-tolerated drug and has statistically significant effects both on cognition and the global clinical status of the participants over 12 and 24 weeks. The improvements as measured by the ADAS-cog were only slightly greater in the 10-mg treated participants than the 5-mg treated participants; however, there were more withdrawals from the high-dose group.

Livingstone and Katona[75]

Although the review did not include mild to moderate severity as an inclusion criterion, all studies reviewed included participants with mild to moderately severe AD and so it is presented here to provide a comparison for the results of the current review. This review also reports trials on rivastigmine (see below), tacrine and huperzine-A, the last two of which were not included in the current review. One study on donepezil met the inclusion criteria of the review and was also included in the current review. The review presents a number-needed-to-treat (NNT) analysis. The review concludes that higher doses of donepezil (10 mg) are associated with lower NNTs.

One additional systematic review, by Birks and Harvey,[76] did not meet the inclusion criteria of the current review as participants were those with mild to moderate or severe dementia. This review was used as a source for references and as a comparator, as the included trials were also included in the current review.

Rivastigmine

Three systematic reviews met the inclusion criteria.

Birks and colleagues[77]

Although the review did not include mild to moderate severity as an inclusion criterion, all studies reviewed included participants with mild to moderately severe AD and so it is presented here to provide a comparison for the results of the current review. Seven studies met the inclusion criteria of the review, and all met the inclusion criteria for the present review. Meta-analyses were undertaken on the outcomes within the trial and a summary is presented here.

Rivastigmine was shown to be beneficial on cognitive measures and activities of daily living measures. Four trials with doses of 6–12 mg/day showed improvement on the ADAS-cog score compared with placebo. In addition, response on the ADAS-cog (<4 points) was also improved in the rivastigmine groups. At the same doses,

improvement was also demonstrated on the PDS in the rivastigmine group compared with the placebo groups. Benefits on a global measure, the CIBIC-plus, were also shown in the meta-analysis.

Wolfson and colleagues[74,78]

This review did not include mild to moderate severity as an inclusion criterion. However, all studies reviewed included participants with mild to moderately severe AD and so it is presented here. This review also reports data for a number of other drugs including donepezil (see above), metrifonate and Ginkgo Biloba; however, the last two do not meet the inclusion criteria of the present review and are not discussed here.

Two studies were included in the review for rivastigmine, both of which are included in the present review. The review reports that the disparate methods of reporting within the included trials made it difficult to compare the magnitude of the results. However, the in-depth review revealed a moderate benefit on both cognition and global clinical status from high-dose treatment with rivastigmine.

Livingstone and Katona[75]

Although the review did not include mild to moderate severity as an inclusion criterion, all studies reviewed included participants with mild to moderately severe AD and so it is presented here to provide a comparison for the results of the current review. This review also report trials on donepezil (above), tacrine and huperzine-A, the last two of which were not included in the present review. Three studies on rivastigmine met the inclusion criteria of the review and were also included in the present review. The review presents an NNT analysis and concludes that higher doses of rivastigmine (6–12 mg) are associated with lower NNTs.

Galantamine

One systematic review met the inclusion criteria for this review.[79] Although the review did not include mild to moderate severity as an inclusion criterion, all studies reviewed included participants with mild to moderately severe AD and so it is presented here. Seven studies were included in the review, of which six provided sufficient outcome data for analysis. The remaining study was published as an abstract, and did not meet the inclusion criteria for the present review. Meta-analyses were carried out and a summary of results is given here to provide a comparison for the results of the present review.

Overall, galantamine showed statistically significant treatment effects at daily doses of 16–32 mg/day for trials of 3–6 months' duration. All six included trials provided global ratings. Trials of 3 months' duration with doses of 24–32 and 36 mg/day were statistically significant in favour of treatment. For trials of 6 months' duration the pattern was the same except with doses of 8 mg/day. Five trials report cognitive function as measured by the ADAS-cog and all daily doses gave statistically significant results at 6 months with the effect size increasing with dose. Results also favoured galantamine on the DAD scale, although only two trials reported this outcome.

Memantine

One systematic review was identified on memantine for dementia.[80] However, it did not meet our inclusion criteria as it consisted of any type of dementia, and not predominantly AD. However, the review does report separately the results for the effect of memantine in participants with moderately severe to severe AD, where only one study, namely that by Reisberg and colleagues,[72] is included.

The review reports that analysis of change from baseline at 28 weeks gave statistically significant results in favour of memantine for 20 mg/day on cognition (6.1, 95% CI: 2.99 to 9.21, $p = 0.0001$), activities of daily living (2.10, 95% CI: 0.46 to 3.74, $p = 0.01$) and in the global clinical impression of change measured by the CIBIC-plus at 28 weeks (0.30, 95% CI: –0.58 to –0.02, $p = 0.04$). In all cases the analysis was an ITT LOCF population. There were no statistically significant differences between memantine and placebo for the number of dropouts and total number of adverse events, but a statistically significant difference in favour of memantine for the number who suffer agitation. The authors conclude that there is a beneficial effect of memantine (20 mg/day) for participants with moderately severe to severe AD on cognition and functional decline but not in the clinical impression of change.

Chapter 6
Economic analysis

Introduction

The aim of this section is to assess the cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for AD. The economic analysis comprises a systematic review of the literature on the cost-effectiveness of these drugs for AD (see Chapter 3 for details), a review of the manufacturer submissions (cost-effectiveness) to NICE and the presentation of cost-effectiveness analysis (CEA) from the current review [Southampton Health Technology Assessment Centre (SHTAC)]. An outline discussion of the literature on costs and health state utilities associated with AD, and the modelling of disease progression over time, is also given.

Cost-effectiveness: systematic review of the literature

Results of literature search

The literature search identified 11 economic evaluations for donepezil,[43,56,81–89] five for rivastigmine,[90–94] five for galantamine[95–99] and three for memantine.[100–102] Two further unpublished papers reporting on the cost-effectiveness of memantine were provided by the manufacturer.[103,104] Also identified were three product-specific systematic reviews[105–107] and three broader systematic reviews[1,78,108] covering the cost-effectiveness of included pharmaceuticals for AD.

Review methods

A review of the cost-effectiveness literature identified is presented. A narrative review focused on the UK cost-effectiveness studies is provided, presenting a separate review for each of the four products, comprising descriptive detail, summary tables and a UK narrative. More detailed information is presented in the Appendices. Where studies are only available as abstracts, outline information is offered but further detail on these studies is not provided. Summary information on the identified product specific systematic reviews, within the appropriate sections, and a general section on systematic reviews covering more than one product are provided. An outline review of the industry submissions (cost-effectiveness) under each of the drug-specific subheadings is given, with further detail on accompanying cost-effectiveness models provided in Appendix 15. Discussion of the associated AD cost studies is focused on those reporting UK cost estimates.

An outline critical appraisal of economic evaluations using a standard checklist[39] is presented and external validity (i.e. the generalisability of the economic study to the UK) using a series of relevant questions (see Appendix 13) is considered. An assessment of the cost-effectiveness models submitted within industry submissions to NICE is provided, using a framework presented by Phillips and colleagues,[109] who have synthesised the literature on the evaluation of decision analytic models in a health technology assessment context to present guidelines for best practice.

Economic evaluations of donepezil

Characteristics of economic evaluations

Table 48 provides a simple summary of the study characteristics for the nine published economic evaluations reporting on the cost-effectiveness of donepezil versus usual care,[43,56,81,82,84–87,89] together with summary detail on two published abstracts.[83,88] The abstracts by Lanctôt and colleagues[83] and Sobolewski and colleagues[88] provide limited information and are not discussed further in this report. Further details of the study characteristics and methods are provided in Appendix 13. Studies represent country-specific analyses for the UK (three studies), Sweden (two studies), Canada (two studies), USA, Japan, Poland and France. *Table 48* reports the 'headline' finding for each study; all studies except the AD2000 study[43] reported drug efficacy either in terms of a delay in disease progression,[56,81,82,84–86,88] quality-adjusted life-year (QALY) gains[83,87] or as reduced time in need of full-time care.[89] In five studies, donepezil treatment was described as cost saving,[83–85,87,89] although all of these studies are from an unclear or societal perspective, whereas in other studies, treatment was described as cost neutral,[82] cost incurring[43,86,88] or cost saving from a societal perspective only (i.e. with savings for patients and caregivers, but not for the healthcare

TABLE 48 *Characteristics of economic evaluation studies for donepezil*

Characteristic	Stein[81]	Stewart *et al.*[82]	Lanctôt *et al.*[83] (abstract only)	Jönsson *et al.*[84]	O'Brien *et al.*[85]	Neumann *et al.*[86]
Publication year	1997	1998	1998	1999	1999	1999
Country setting	UK	UK	Canada	Sweden	Canada	USA
Base year prices	? 1996 or 1997 (UK£)	? 1996 or 1997 (UK£)	? (Can$)	? 1995, (drugs 1998) (SEK)	1997 (Can$)	1997 (US$)
Intervention	Donepezil 5, 10 mg	Donepezil 5, 10 mg	Donepezil, unspecified dose	Donepezil 5, 10 mg	Donepezil 5 mg	Donepezil pooled 5- and 10-mg doses
Study type	CUA by simple calculation	CEA model	CEA model	CEA model	CEA model	CUA model
Study group – AD	Mild to moderate	Mild to moderate	Mild	Mild to moderate	Mild to moderate	Mild to moderate
Perspective	Not stated (appears to be health sector)	Not stated (appears to be societal)	Not stated	Not stated (appears to be health and social care sectors)	Stated – societal	Stated – societal
Industry role	None disclosed	Not stated – two authors and some data from Pfizer	None disclosed	Funded by Pfizer	Funded by Pfizer	Funded by Pfizer
Study base-case 'headline' predictions/ findings	Delay in cognitive decline, with additional costs (analysis limited to drug costs only)	Reduced time in severe AD state, approximately cost neutral for both doses over 5 years	Current information does not allow consistent conclusions to be drawn	Increased time in non-severe AD states, cost savings over time	Reduced time in severe AD state, cost saving over 5 years	Delay in disease progression, QALY gains, base case not cost saving over 18 months

	Ikeda *et al.*[87]	Sobolewski *et al.*[88] (abstract only)	Fagnani *et al.*[89]	Wimo *et al.*[56]	AD2000 Collaborative Group[43]
Publication year	2002	2002	2003	2003	2004
Country setting	Japan	Poland	France	Sweden	UK
Base year prices	2000 (Yen)	? (zl/US$)	? (Euro)	1999 (SEK, US$)	? 2000 (£)2002–03 (UK£)
Intervention	Donepezil 5 mg	Donepezil 5, 10 mg	Donepezil 10 mg	Donepezil 5, 10 mg	Donepezil 5, 10 mg
Study type	CEA model (CUA)	CEA model	CMA model	Cost – consequence analysis	EEACT
Study group – AD	Mild to moderate	Mild to moderate	Mild to moderate	Mild to moderate	Mild to moderate
Perspective	Stated – payer	Stated – societal	Stated – societal	Stated – societal	Stated – societal
Industry role	None disclosed	None disclosed	Funded by Eisai Laboratoires, France	Supported by Pfizer Pharmaceuticals Group	None
Study base-case 'headline' predictions/ findings	QALY gains, cost saving over 2 years	Increased time in non-severe AD state, not cost saving	Reduced time in need of FTC, cost savings over 3 years	Delay in loss of activities of daily living, cost saving to patients/caregivers over 1 year	Donepezil is not cost-effective

?, Unclear information reported; CEA, cost-effectiveness analysis; CUA, cost–utility analysis; EEACT, economic evaluation alongside clinical trial; FTC, full-time care.

system or social services).[56] In one study, treatment costs were unclear owing to a lack of data.[81] Further detail on study findings is provided in Appendix 14.

Systematic reviews on the cost-effectiveness of donepezil

One product-specific systematic review was identified[105] to inform on the cost-effectiveness of donepezil; it included three published economic studies[82,85,86] and one abstract.[83] These published studies are discussed in the review below. Foster and Plosker[105] report that two of the studies indicated that treatment was associated with a slight increase in overall treatment costs and two indicated a slight decrease in overall treatment costs, with all stating that donepezil treatment produced a better outcome than no donepezil treatment for patients with mild-to-moderate AD. However, the authors pointed out that there was a considerable degree of uncertainty within study results.

Estimation of outcomes within economic evaluations (donepezil)

Most economic evaluations of donepezil (six of the nine published studies[82,84–87,89]) have used a state transition model (Markov model) to simulate disease progression in their estimation of the cost-effectiveness of donepezil. The models are summarised in the following section. Stein[81] reports a simple cost calculation, Wimo and colleagues[56] report a cost–consequence analysis alongside the findings from a clinical trial and the AD2000 Collaborative Group[43] report an economic evaluation alongside a clinical trial to consider the cost-effectiveness of donepezil.

Cost-effectiveness models for donepezil

Table 49 presents outline detail on the approaches used to model disease progression and the subsequent cost-effectiveness of donepezil. All approaches modelled disease progression for a specified cohort of AD patients across different levels of disease severity (including an ongoing risk of death). Three studies used MMSE scores to define either four or five levels of AD severity,[82,84,85] two studies used CDR scores to define three levels of disease severity[86,87] and one study[89] was developed using the continuous nature of the MMSE scoring system. Progression of disease was modelled using transition probabilities between each model cycle to estimate the likelihood that a patient moves from one level of disease severity to another, with an ongoing risk of death over time. There are variations between studies in the methods used to determine appropriate transition probabilities for the disease progression models. Three studies obtained transition probabilities for donepezil-treated and untreated groups from clinical trial data,[84,85,89] one study[82] used epidemiological data for the untreated group and trial data for the donepezil treated group and the others used epidemiological data to calculate transition probabilities for the untreated group and then applied a risk reduction factor derived from clinical trial data to generate transition probabilities for the treatment group.[84,86,87] In some studies the effect of donepezil on disease progression was assumed to last for only part of the overall time horizon,[82,85,89] but other studies assumed that the treatment effect persisted for the entire time horizon.[84,86,87] Generally models incorporated an on-going mortality risk that was the same for both treated and untreated patients; this mortality risk was dependent on disease severity in three studies.[84,86,87] Cycle length, time horizon and the characteristics of the baseline patient cohorts varied across studies (see *Table 49*). All the studies assumed that donepezil treatment would stop when patients reached a state of severe AD.

Estimates of outcomes

Study outcome estimations are presented in Appendix 14. The main outcome measures are reduced time in the severe AD state (delay in disease progression) and/or QALY gains.

The 1997 UK report prepared by Stein[81] presents cost–utility estimates based on drug costs only. The lack of comprehensive information on service use and costs at the time meant that the author was unable to offer an appraisal of the full economic effects of donepezil and no modelling was undertaken. Cost–utility estimates are provided for 5 and 10 mg donepezil in patients with mild to moderate AD with four possible estimates of treatment duration considered: 2, 5, 8 or 10 years. QALY gains that may accrue as a result of a 6-month delay in disease progression were estimated by the author. Stein used the Index of Health Related Quality of Life (IHQL) and made assumptions regarding the classification of patients on the physical, disability and emotional dimensions of the index and the impact that a 6-month delay in disease progression may have. This enabled a QALY gain to be estimated, thought to lie between 0.05 and 0.08, but since the IHQL is not validated for valuing cognitive impairment and the classification of patients was determined (estimated) by Stein (and colleagues), these QALY values should be regarded as purely speculative.

TABLE 49 *Outline detail on the modelling methods/structure used in the cost-effectiveness literature for donepezil*

	Stewart *et al.*, 1998[82]	**Jönsson *et al.*, 1999[84a]**	**O'Brien *et al.*, 1999[85]**	**Neumann *et al.*, 1999[86]**	**Ikeda *et al.*, 2002[87]**	**Fagnani *et al.*, 2003[89]**	**Industry submission**
Severity levels	4 levels by MMSE score: minimal 21+ mild 15–20 moderate 10–14 severe <10 plus an absorbing state (dead)	5 levels by MMSE score: 1. 27–30[b] 2. 21–26 3. 15–20 4. 10–14 5. 0–9 plus an absorbing state (dead)	5 levels by MMSE score: 1. 27–30 2. 21–26 3. 15–20 4. 10–14 5. <10 plus an absorbing state (dead)	3 levels by CDR score: mild (Mi) 0.5 or 1 moderate (Mo) 2 severe (S) 2 settings within each level: community (C) or nursing home (N), and an absorbing state (dead)	3 levels by CDR score: mild moderate severe plus an absorbing state (dead)	By MMSE score (categories not specified/used)	4 levels by MMSE score: minimal 21+ mild 15–20 moderate 10–14 severe <10 plus an absorbing state (dead)
Time horizon	5 years	5 years	5 years	18 months	2 years	3 years	5 years
Cycle length	6 months	6 months	6 months	6 weeks	4 weeks	6 months	12 months
Patients in the model	Two subgroups evaluated: 1. All mild AD at start 2. All moderate AD at start Baseline characteristics not described	*Kungsholmen analysis* Data were taken from the Kungsholmen project *Within-trial analysis* Initial cohort distribution from Kungsholmen project and simulations undertaken for a patient aged 84.5 years at start (mean age of the Kungsholmen group)	Initial MMSE score between 10 and 26 with distribution of MMSE scores based on a Canadian cohort study[114] used as a weighting factor	Two subgroups evaluated: 1. All mild AD in the community at start 2. All moderate AD in the community at start Baseline characteristics not described	Two subgroups evaluated: 1. All mild AD at start 2. All moderate AD at start Baseline characteristics not described	Initial MMSE score between 10 and 26. Baseline age distribution similar to that in the Winblad trial (Winblad *et al.*, 2001[47]) Baseline residential status as a function of MMSE score based on French prevalence studies[115–117]	Hypothetical cohort of 300 patients with 100 patients in each of the AD states minimal, mild and moderate. Baseline characteristics not described

continued

TABLE 49 *Outline detail on the modelling methods/structure used in the cost-effectiveness literature for donepezil (cont'd)*

	Stewart *et al.*, 1998[82]	**Jönsson *et al.*, 1999[84a]**	**O'Brien *et al.*, 1999[85]**	**Neumann *et al.*, 1999[86]**	**Ikeda *et al.*, 2002[87]**	**Fagnani *et al.*, 2003[89]**	**Industry submission**
Cost inputs summary	Values for cost inputs are not given although the sources of the cost information used are cited[118–120]	Mean total annual costs (SEK) by severity group Gp1 18,699 Gp2 55,437 Gp3 190,307 Gp4 273,086 Gp5 450,702	Expected costs (Can$) per 6-month cycle by MMSE score 21–26 3,719 15–20 6,754 10–14 10,765 <10 16,342	Costs (US$) by stage and setting Mi/C 46,277 Mi/N 46,776 Mo/C 56,559 Mo/N 57,170 S/C 65,695 S/N 66,404	Values for cost inputs are not given although the values from which cost inputs were calculated are provided	Monthly costs (Euro) by MMSE score: Home care >20 192 16–20 659 11–15 1319 ≤10 4105 Non-medical/medical institution >20 682/891 16–20 923/1131 11–15 1083/1292 ≤10 1340/1548	Total annual costs (UK£) by severity group (excluding drug cost) Severe £25,488 Moderate £17,950 Mild £13,327 Minimal £9,515

[a] Performed the Kungsholmen analysis and a within-trial analysis.
[b] Not used in the Kungsholmen analysis.

The UK study reported by Stewart and colleagues[82] presents the results of modelling a comparison of 5 and 10 mg donepezil and placebo in patients with (1) mild AD and (2) moderate AD. Effectiveness for donepezil is integrated using trial data from Rogers and colleagues[51] in the first 6-month cycle of their model. Thereafter transition probabilities are assumed to be equal for donepezil-treated and untreated groups. Once patients reach a state of severe AD, donepezil treatment is stopped and transition probabilities describing disease progression from this point (severe AD) are based on disease progression of untreated patients reported in a UK observational study, the Cambridge cohort study.[111] The model uses a 5-year time horizon, 6-monthly cycles and a constant mortality rate (derived from a rate of 53% over 3 years[112,113]) in each cycle.

Stewart and colleagues[82] report that treatment with 5 mg donepezil in patients with mild AD resulted in an estimated 1.69 years in a non-severe health state, in comparison with 1.57 years in the placebo group; 10 mg donepezil resulted in an estimated 1.82 years in a non-severe AD health state. Analysis for moderate AD estimated 0.98 years in a non-severe AD health state for the 5-mg donepezil group, 0.87 years for the 10-mg donepezil group and 0.59 years for the placebo group.

The AD2000 Collaborative Group[43] report that no statistically significant benefits were seen with donepezil compared with placebo, in terms of rates of institutionalisation or progression of disability, even though cognition averaged 0.8 MMSE points better and functionality 1.0 BADLS points better with donepezil over the first 2 years. There were also no statistically significant differences between the 5- and 10-mg donepezil doses (further discussion of the study findings can be found in Chapter 4).

Studies by Jönsson and colleagues,[84] O'Brien and colleagues,[85] Neumann and colleagues[86] and Ikeda and colleagues[87] also use a state transition modelling approach but with variations in the patient cohorts that enter the model, the transition probabilities used to describe disease progression, the mortality rates used, the length of each cycle in the model and the overall time horizon of the model. Model characteristics and findings for these non-UK studies are reported in *Tables 48* and *49*, with further details in Appendix 13.

Estimation of costs within economic evaluations (donepezil)

The modelling studies discussed above assigned costs within the modelling process, by cycle, according to health states describing disease severity. Wimo and colleagues[56] assigned costs according to data collected from caregivers in a 12-month trial (using the Resource Utilization in Dementia questionnaire). The AD2000 trial[43] collected resource use data prospectively within the trial protocol. In their estimation of resource use and AD cost, studies used various country-specific data sources for resource use and unit costs, there is variability in the cost elements that are included in studies, and further details are provided in Appendices 13 and 14.

Stein's UK report[81] calculated drug costs of £1732 over 2 years for a 5 mg/day dose of donepezil, rising to £9736 over 10 years for the 10 mg/day dose (discounted at 6%). Additional NHS costs associated with increased specialist referral and computed tomography (CT) scanning of AD patients on donepezil were estimated. However, as the existing levels of service use and the impact that donepezil would have on this were unknown the assumed additional NHS costs were described as illustrative. These additional costs ranged from £264 over 2 years to £637 over 10 years (discounted at 6%). A number of costs relating to changes in service use, costs falling on residential care services, social services, voluntary agencies and informal caregivers could not be evaluated at the time of the report because of a lack of available information.

The UK study by Stewart and colleagues[82] used cost data from earlier work at the Personal Social Services Research Unit (PSSRU)[118–120] which estimated the costs associated with typical care packages provided for elderly people with different levels of dementia. These costs had been updated by Stewart[121] to 1996 price levels and applied to four levels of dementia severity based on MMSE scores [mapped from SEVINT, an Office of Population Census and Surveys (OPCS) measure of intellectual functioning]: minimal, mild, moderate and severe. Details of the PSSRU studies and the methods by which costs were updated are not provided, although the relevant papers are cited.

Stewart and colleagues[82] report the expected 5-year cumulative costs (further updated to UK£ 1997) per patient for those patients mild at onset were £44,277 for the placebo cohort, £45,119 for the donepezil 5-mg treatment cohort and £45,694 for the donepezil 10-mg treatment cohort. With cost differences of around £1400 over 5 years, the authors described this as an almost neutral cost

outcome. The incremental cost per extra year in a non-severe AD health state was £7047 for the 5-mg dose versus placebo and £5697 for the 10-mg dose versus placebo. The incremental cost per extra year in a non-severe health state for the 10-mg dose versus the 5-mg dose was £4450. For those patients with moderate AD at the start of the model the expected 5-year cumulative costs per patient were £45,719 for the placebo cohort, £46,193 for the donepezil 5-mg treatment cohort and £46,716 for the donepezil 10-mg treatment cohort.

The AD2000 Collaborative Group[43] collected resource use data prospectively as part of the trial in order to calculate an average annual cost per patient. Data are reported against 11 formal health and social services. Cost estimates do not include the cost for donepezil or costs associated with institutionalisation. Although not explicitly stated, costs are presented as 2000£. The reported estimated annual cost per patient resident in the community in the donepezil group was £2842 and in the placebo group £2344; the annual additional cost with donepezil was £498 (–193 to 1189). Cost estimates are not presented separately by dose but authors report that the costs (of care) for 5-mg donepezil were £445 higher than the 10-mg dose. None of the differences on resource use (or cost) were statistically significant

Cost-effectiveness of donepezil – summary results

Appendix 14 presents summary findings on the cost-effectiveness of donepezil across all included studies. Studies generally report cost savings over time with patient benefits in terms of a delay in disease progression (using MMSE scores to define stages of disease severity), with more time spent in the less severe AD health states. However, many of the studies report findings based on a societal perspective, including patient and caregiver costs. The findings from the UK cost-effectiveness studies are summarised below.

Stein[81] presents costs per QALY estimates based on applying only drug costs. A gain of between 0.05 and 0.08 QALYs is estimated based on assumptions for the level of benefits gained from treatment. A cost per QALY of £34,640 is predicted for a 5 mg/day dose over 2 years when treatment is assumed to give a benefit equivalent to 0.05 QALY, rising to £79,560 for 5 years, £117,280 for 8 years and to £139,020 for 10 years. Increasing the benefit to 0.08 QALY reduces the cost per QALY to £21,383 over 2 years, rising to £85,815 for 10 years of treatment. Stein also provides cost–utility estimates for a 10 mg/day dose of donepezil stating that the evidence for marginal benefit over the 5 mg/day dose is less clear than the evidence for the dis-benefits that are associated with the higher dose. With an assumed benefit of 0.05 QALY the cost per QALY of a 10 mg/day dose is £48,500 over 2 years of treatment, rising to £194,720 for 10 years. The higher QALY gain assumption of 0.08 reduces the cost per QALY to £29,938 for 2 years and £120,198 for 10 years.

Stewart and colleagues[82] present results as incremental investment in treatment required to achieve an extra year spent in a non-severe AD state. Treatment groups are described as being almost cost neutral over the 5-year time horizon as costs are raised only very slightly. Two treatment groups are considered: patients who have mild AD at the start of treatment and patients who have moderate AD at the start of treatment. For patients with mild AD who are treated with donepezil at the 10-mg dose, an incremental cost (over placebo) of £5698 is required to obtain an extra year in a non-severe AD state and the incremental cost versus the 5-mg dose is £4451. For patients with mild AD who are treated with the lower 5-mg dose an incremental cost (over placebo) of £7048 is required to obtain an extra year in a non-severe AD state. If the patients entering the model have moderate AD then an incremental cost (over placebo) of £3562 is required to obtain an extra year in a non-severe AD state when they are treated with a 10-mg dose and there is no incremental benefit versus the 5-mg donepezil dose. If they are treated with the 5-mg dose an incremental cost (over placebo) of £1210 is required to obtain an extra year in a non-severe AD state.

Stewart and colleagues[82] also ran sensitivity analyses in which some parameter inputs for the model were altered. They report that variations in the discount rate do not cause any alteration in the relative positions of the AD subgroups. A lower mortality rate (30% over 3 years) which leads to more patients remaining alive at later stages and continuing to incur costs was also tested. With this lower mortality rate the incremental costs (over placebo) for an additional year in a non-severe AD state reduce slightly to £4955 and £5328 for the 10- and 5-mg donepezil groups, respectively, in mild AD. In moderate AD the incremental costs for the 10- and 5-mg doses are £3372 and £942, respectively. No other sensitivity analyses are reported.

The AD2000 study[43] presents results indicating that usual care alone is the dominant strategy over treatment with donepezil plus usual care; with no statistically significant benefits in institutionalisation or progression of disability (the two primary effectiveness outcomes) and an estimated additional annual cost per patient. The AD2000 study reports that donepezil is not cost-effective with benefits below minimally relevant thresholds.

AD2000 reports sensitivity analysis, comprising multivariate analyses, which indicates that improvements in functional ability with donepezil (assuming the maximum benefit compatible with the trial data) would not delay institutionalisation sufficiently to offset the costs of the drug. The authors state that the impact of variations in key variables was tested but this is not reported in detail in the published paper. The authors report that there were no plausible valuations of unpaid caregiver time that would offset the higher costs of formal care seen with donepezil.

Industry submission on cost-effectiveness of donepezil

In their submission to the NICE technology appraisal process, the manufacturer of donepezil (Eisai/Pfizer) presents cost-effectiveness analysis for donepezil (5 mg for 28 days and 10 mg thereafter) plus usual care compared with usual care alone in the UK. The submission presents findings from a model developed to estimate the cost-effectiveness of donepezil over a 5-year period.

The submission details a transition-state modelling approach in which disease progression is modelled across different levels of AD severity for a hypothetical cohort of 300 patients with minimal, mild, and moderate disease (100 patients each group). AD severity is defined by MMSE score and disease progression is modelled using transition probabilities in each cycle of the model to estimate the likelihood that a patient moves from one level of disease severity to another. Patients tend to progress toward more severe states of AD although movement back to previous less severe states is possible for those in the mild and moderate groups. In the base-case analysis transition probabilities are derived from trial data[47] with the drug efficacy rate persisting for the initial 12-month cycle of the model. Thereafter the 12-month transition probabilities for the treated group are proportional to those of the placebo group such that by the end of the time horizon treated and untreated groups are at the same MMSE level [this is the base-case scenario (c)]; other scenarios are considered in sensitivity analyses. The mortality rates for patients with minimal, mild or moderate AD were derived from trial data.[47] The mortality rate for severe AD was from the published literature at 11% per year.[129] Donepezil treatment ceases once a patient's MMSE score reaches 12 or below (as this is what NICE guidance currently states), although results are also presented for treatment up to an MMSE score of 10.

The model incorporates cost data from Wolstenholme and colleagues,[122] who calculated costs of care for different severity levels of AD by MMSE score [see the section 'Costing considerations in the treatment of AD (p. 108) for further discussion]. Costs from Wolstenholme and colleagues are updated to 2002–03 prices using the Hospital and Community Health Services pay and prices index.

The industry submission reports that for their base case (patients with MMSE scores of 13–26), treatment with donepezil results in an estimated mean difference of 0.1523 years per patient in a severe AD health state. Cost estimates show an expected additional cost per patient of £183.78. Cost-effectiveness results are reported using time in a non-severe health state as the outcome. The base-case analysis reports at £1206 per year in non-severe AD for donepezil versus placebo, with the incremental cost-effectiveness ratio (ICER) increasing to £3956 where treatment covers patients with MMSE of 10–26 (base case is MMSE range 13–26). In addition to base-case results, the submission reports findings where the model incorporates a half-cycle correction (to make some allowance for the 12-month cycle used in the model), and in this scenario the cost per year in a non-severe state is reported at £7449 (for patients with MMSE 13–26); results are not reported for a treatment range of MMSE 10–26, but presumably these would be higher.

Probabilistic sensitivity analysis on randomly selected transition probabilities and costs gave a mean positive ICER of £3278 (95% CI: –£16,307 to £33,148) for base-case analysis; with half-cycle correction included the cost per year in a non-severe AD health state is reported at £10,826 (95% CI: –£9182 to £53,907); (we would suggest that with an incremental utility of 0.30 between severe and non-severe AD this ICER estimate of £10,826 is interpreted as somewhere in the region of £36,000 per QALY). Once again we assume that with an MMSE treatment range of 10–26 this estimate would increase.

Cost-effectiveness acceptability curves (CEACs) indicate (reading from figures only) that the probability that the ICER for donepezil at base case would be dominant in favour of donepezil is 37%, and where half-cycle corrections are applied the probability of a dominant ICER is around 15%. However, these data are not specified, and we are unsure how the analyst has interpreted ICERs to determine the CEACs (i.e. a negative ICER can have different interpretations – negative benefits and additional costs gives an ICER below zero).

The CEAC with half-cycle correction indicates a probability of around 55% of getting an ICER at £15,000 per year of non-severe AD (we would suggest that with an incremental utility of 0.30 between severe and non-severe AD this is interpreted as somewhere in the region of £50,000 per QALY).

One-way sensitivity analyses are reported against discount rate, disease progression, source of cost data and mortality rate. Results were sensitive to assumptions made about disease progression, source of cost data and mortality rate. The ICER increased significantly assuming that benefits of drug treatment were reflected in transit probabilities for the first 12-months only [scenario (a)] (ICER £23,162) and ICERs also increased with alternative cost sources. Using higher mortality rates resulted in cost dominant ICERs (–£1324 to –£2208). (Sensitivity analysis not reported for half-cycle correction scenario.)

Comments on industry submission

The CEA in the industry submission for donepezil is based on a model that is solely structured around cognitive function using the MMSE (see Appendix 15 for an outline appraisal of the model). Health states for stages of disease severity are described using categories of MMSE, and transitions between these health states are based on patient level MMSE data from one clinical trial: the RCT reported by Winblad and colleagues[47] with 286 patients randomised to either donepezil or placebo (across 28 treatment centres). The authors do not provide a rationale for the model structure. The transit probabilities used remain unpublished (presented in industry submission), and the data used to derive them have not been published. Winblad and colleagues report a statistically significant difference in MMSE over 52 weeks (–0.46 donepezil versus –2.18 placebo); however, analysis is not based on ITT and MMSE is a secondary outcome measure. Primary outcomes were GBS (not statistically significant) and GDS (where a statistically significant improvement was shown).

Although accepting that there are currently few alternatives to the use of cognitive function when considering AD progression, we believe that it is important to state that the use of cognitive function alone (i.e. MMSE in this model) is likely to misrepresent disease progression over time. In this instance the use of transit probabilities from this one clinical trial introduces added uncertainty over the methods used to model disease transition over time (by defined health states), given the documented concerns over the use of the MMSE.[43,123–125]

When comparing the transit probabilities used to predict disease progression in donepezil-treated patients versus placebo, we note that there are a number of instances where large differences occur in the probabilities associated with moves between health states, for example, the probability of patients remaining in a minimal severity AD state (82% donepezil versus 69% placebo per year), the predicted move from mild AD back to minimal AD (26 versus 2%) and the predicted move from mild AD to severe AD (2 versus 17%). Given that the mean difference between donepezil and placebo in MMSE score per year is 1.72 points in the clinical trial, and that there are no data published presenting the numbers of patients involved in transits between health states, we would raise concerns over the use of the data to predict disease progression in a broader treatment eligible population, that is, numbers may be small and differences may be statistically insignificant, and thereafter is the common issue of transferring findings from a clinical trial setting to general practice.

Furthermore, we have concerns over the endpoint used in the model, namely time in years spent in an AD health state that is non-severe (i.e. <10 or 12 MMSE score) and the impact of mortality on this endpoint. In the base-case analysis, there is an almost zero mortality risk for those in a non-severe state, and this applies over the 5-year timeframe; we believe this to be incorrect and that over 10% of patients will die each year (i.e. standard all-cause mortality for the UK population aged 75–84 is in excess of 7% per year). For the cohort of 300 patients used in the industry model we would expect around 30–50% of these to have died over the 5-year period. In practice we would expect a position where a proportion of patients will be treated but will die before long-term benefits are realised (assuming benefits accrue over the longer

term). Where we see no mortality effect in the model of disease progression we are in effect seeing a greater number of years lived in a non-severe AD state than would actually be expected. However, we are concerned that where mortality is introduced to the model it has a perverse effect on the endpoint used (i.e. sensitivity analysis shows an incremental cost saving and slight change in incremental benefits compared with base case, although absolute data are not presented). Where Stewart and colleagues[82] used a similar modelling approach they report that increasing mortality results in a higher cost per year of non-severe AD.

Within the model (and base-case results) presented we are concerned at the use of a 12-month cycle (to fit with data from the 1-year trial) given the differences presented in the industry submission when half-cycle correction has been employed. In a Markov model using a 12-month cycle, events (transits between states of disease severity) are assumed to occur at the end (or start) of the 12-month cycle. Where a half-cycle-correction is applied, there is an allowance for events occurring mid-cycle, and this can impact on the expected value for costs and benefits. The industry submission reports findings to indicate that the impact of the half-cycle correction in this model is very significant, yet the base-case results presented and the presentation of most findings in the sensitivity analysis are not calculated using the half-cycle correction. We believe the appropriate findings are those that make some allowance for events within the 12-month cycle period. This alters the base-case ICER from £1206 per year in a non-severe AD state to £7449 per year (£3278 and £10,826, respectively, for probabilistic analysis). Results reported using half-cycle correction show an increase in incremental costs incurred and a reduction in incremental benefits gained (years in non-severe state), compared with base-case analysis. The authors of the industry submission attribute these marked differences to entry and exit rates (transit probabilities) from the health state 'minimal AD', where data predictions are very different for the donepezil and placebo cohorts.

Where the industry submission examines sensitivity analysis, it notes a large impact on cost-effectiveness where assumptions on effectiveness are relaxed (i.e. where effect is assumed to last for 1 year only [scenario (b)] the ICER increases to over £23,000 per year in a non-severe state). Scenario (a), where probabilities are different for the first 12 months, and thereafter patients transit by the same transit probability matrix, is presented as a cost-saving scenario.

Within the industry model, we have concerns over the mortality data used. As discussed above, the transition probability matrix in the model makes minimal allowance for transit to death from AD states. In the donepezil treated cohort the probability of moving to death from the minimal and mild AD states is zero and from moderate AD the probability of death is 5% per year. In the usual care cohort, the probability of death from minimal AD is zero, from mild AD it is 2% per year and from moderate AD it is zero. These data highlight concerns with generalisability from the trial data used in the model. Sensitivity analysis is reported for mortality rates included, with increases in mortality resulting in a more attractive profile for donepezil treatment, and we have raised concerns over this above.

Cost estimates used in the model are from data derived and presented by Wolstenholme and colleagues[122] [discussed in the section 'Costing considerations in the treatment of AD' (p. 108)], and although these may reflect resource use in the sample studied by those authors, the study does not take into account that not all costs are met by the NHS and Personal Social Services (PSS), with many patients in an institutional setting being privately funded (or at least partially funded from private sources). Furthermore, where publicly funded patients are also in receipt of state pension payments, these will be used as a transfer payment to offset funding in an institutional setting [for further discussion of this issue, see the section 'Costing considerations in the treatment of AD' (p. 108)]. The study by Wolstenholme and colleagues, used in the base-case analysis, is unclear as to where the costs for private accommodation are factored into analysis. If costs for personal accommodation are included in the analysis the perspective of the study is not that of the NHS and PSS, and the cost data will be incorrect for the analysis in the donepezil model.

The executive summary in the industry submission states that "Donepezil costs can be fully offset (i.e. cost saving), generally after two years of treatment", but this result is not presented in the report and the scenarios tested by the model indicate that many of the 5-year outcomes are cost incurring.

See our adjustments to the industry model in the section 'SHTAC analysis of cost-effectiveness of donepezil, rivastigmine and galantamine using the industry models submitted to NICE (p. 131).

Economic evaluations of rivastigmine

Characteristics of economic evaluations

Table 50 provides a summary of the study characteristics for the four published economic evaluations reporting on the cost-effectiveness of rivastigmine,[90–93] together with summary detail on one published abstract.[94] The abstract by Brooks and Deal[94] provides limited information and is therefore not discussed further in this report. Published studies present country-specific analyses for the UK (two studies), the USA and Canada. The headline findings across published studies are a delay in disease progression and cost savings over time. Further details on study characteristics and methods are provided in Appendix 13 and further detail on study findings is provided in Appendix 14.

Systematic reviews on the cost-effectiveness of rivastigmine

Only one systematic review on the cost-effectiveness of rivastigmine (alone) was identified, by Lamb and Goa.[106] This included three published economic studies,[91–93] and one conference abstract.[94] These published studies are discussed in the review below. Lamb and Goa[106] summarise these studies and draw the conclusion that rivastigmine offsets the costs of treatment (either partially or completely) by delaying cognitive decline and the time to institutionalisation in patients with mild-to-moderate AD. They conclude that the greatest cost savings (from a societal perspective) are likely to be realised when drug treatment starts in the early stages of the disease. However, they point out that the conclusions are dependent on extrapolating from 6-month trial data and warn that study results should be viewed with caution.

Estimation of outcomes within economic evaluations (rivastigmine)

The study by Stein[90] used a simple decision analysis approach to consider outcomes, calculating numbers needed to treat for five definitions of clinically important treatment effects and estimating cost per QALY. Three of the four

TABLE 50 *Characteristics of economic evaluation studies for rivastigmine*

Characteristic	Stein[90]	Fenn and Gray[91]	Hauber *et al.*,[92]	Hauber *et al.*,[93]	Brooks and Deal[94] (abstract only)
Publication year	1998	1999	2000	2000	2000
Country setting	UK	UK	USA	Canada	USA
Base year prices	?1996/1997 UK£	1997 UK£	1997 US$	1997 Can$	Not reported
Intervention	Rivastigmine 6–12 mg	Rivastigmine low dose (1–4 mg), high dose (6–12 mg)	Rivastigmine unspecified dose	Rivastigmine pooled low (1–4 mg) and high (6–12 mg) doses	Rivastigmine dose not reported
Study type	CUA by simple calculation	CEA model	CEA model	CEA model	CEA model
Study group – AD	Mild to moderate	Mild and moderate	Mild and moderate	Mild, mild-to-moderate and moderate	Mild and moderate
Perspective	Not stated (appears to be health sector)	Stated – health and social care systems	Not stated (unclear)	Stated – societal	Not stated
Industry role	None disclosed	Supported by Novartis Pharma, Switzerland	Funded by Novartis Pharmaceuticals, USA	Funded by Novartis Pharmaceuticals, Canada	Not reported
Study base-case 'headline' predictions/findings	Delay in cognitive decline, with additional costs (analysis limited to drug costs only)	Cost savings over time, set against reported clinical benefits	Delay in cognitive decline and cost savings over time	Delay in cognitive decline and cost savings over time	Cost savings over time

published economic evaluations of rivastigmine[91–93] use a hazard model to examine disease progression in their estimation of the cost-effectiveness of rivastigmine. This hazard model was developed by Fenn and Gray,[91] and is discussed further below.

Fenn and Gray hazard model of disease progression

The hazard model of disease progression uses individual patient data[57,58] to estimate the time taken for each patient to move from one level of AD severity to another. The model estimates the likelihood that a patient will remain at a particular MMSE score at any given time. Statistical techniques are used to model disease progression. In brief, linear interpolation was used to calculate the timing of each one-point drop in MMSE scores, based on the intervals between clinic visits in trial data, in order to calculate the time taken for a patient with a particular MMSE score at baseline to move to the next AD severity level. The model is used to generate survival curves for both placebo and rivastigmine treatment groups, with these extrapolated beyond the end of the trial period. The impact of treatment on disease progression is measured as days saved by preventing patients from entering the next, more severe stage of AD. This delay in disease progression is represented by the area between the placebo and treatment survival curves. The hazard model does not incorporate a mortality risk directly in the disease progression process. The proportional difference in cognitive decline between the placebo and treatment groups estimated by the model is assumed to persist until patients reach the most severe stage of disease at which point the treatment effect declines to zero.

Fenn and Gray,[91] and Hauber and colleagues[92,93] use the same trial data[57,58] to populate their respective cost-effectiveness models; however, only the two studies by Hauber and colleagues[92,93] report in detail the delay in cognitive decline (additional days in a less severe AD state) due to rivastigmine treatment. The study by Fenn and Gray,[91] although discussing costs and consequences, is primarily a methodological study reporting the design and development of the hazard model for AD.

Estimates of outcomes

Two studies report on the cost-effectiveness of rivastigmine in the UK. Stein[90] estimates cost–utility by simple calculations, whereas Fenn and Gray[91] apply the hazard model discussed above.

Stein[90] presents NNT analysis for the effects of rivastigmine and cost–utility estimates based on drug costs only. At the time of the report (1998), service costs associated with the use of rivastigmine could not be predicted with precision and therefore the author did not offer an appraisal of the full economic effects of rivastigmine and no modelling was undertaken. The NNTs were calculated from pooled analyses of three clinical trials for five definitions of clinically important treatment effects based on outcomes on the ADAS-cog, CIBIC-plus and PDS measures. The calculated NNTs ranged from 9 to 25 but since the thresholds for clinical significance were unknown to Stein he emphasises that these outcomes should be viewed with caution. Cost–utility estimates are provided for rivastigmine at either 6- or 12-mg doses (unit costs for both preparations were the same) in patients with mild to moderate AD with three possible estimates of treatment duration considered: 1, 2 and 5 years. The QALYs gains that may accrue as a result of a 6-month delay in disease progression were estimated using the same rationale as described above for Stein's report on donepezil. A QALY gain, of between 0.05 and 0.08, was assumed but again these values should be regarded as purely speculative.

Fenn and Gray[91] report the results of their hazard model approach, comparing rivastigmine treatment (either high or low dose) with placebo. The distribution of baseline MMSE scores were from trial data,[57,58] where patients with an MMSE score of <10 had been excluded. The mean MMSE score was 19.9 ± 4.49 (n = 1333). Levels of disease severity (model health states) were defined according to MMSE scores: mild 30–21, moderate 20–11 and severe 10–1. The treatment effects for high-dose rivastigmine were statistically significant and an example of the differences between disease progression in the treatment group in comparison with placebo was presented by Fenn and Gray[91] in a figure where the area between the high-dose treatment curve and the placebo curve represents the number of additional days that the patient remains in the less severe disease stage. Numerical values for days saved are not presented separately.

Studies by Hauber and colleagues[92,93] use the same model and incorporate the same clinical trial data as Fenn and Gray.[91] Hauber and colleagues[92] define the same three disease stages as those used by Fenn and Gray[91] (although the range of MMSE scores for severe extends from 10 to 0) and therefore the estimates of the delay in cognitive decline observed with rivastigmine

treatment should be the same as those calculated by Fenn and Gray.[91] Hauber and colleagues[92] estimated that trial participants with mild baseline disease severity would spend an additional 4 days in the mild stage but no additional days in the moderate stage during a 6-month time horizon. Extending the time horizon to 2 years increased the estimated additional days in the mild stage to 56 days and then once in the moderate stage an additional 69 days is spent here, giving a total of 125 extra days in total in a non-severe stage of disease. For those patients with moderate baseline severity an estimated 51 additional days would be spent in moderate severity AD over a 2-year time horizon in comparison with those in the placebo group. In the Hauber and colleagues[93] study, four disease stages are defined so the findings are slightly different. Further details on the study methods are reported in Appendix 13, with findings for the non-UK studies in Appendix 14.

Estimation of costs within economic evaluations (rivastigmine)

Stein's UK report[90] calculated drug costs of £821 over 1 year rising to £3666 over 5 years for both doses of rivastigmine (6- and 12-mg doses cost the same and costs discounted at 6%). Additional NHS costs associated with increased specialist referral and CT scanning of AD patients on rivastigmine were estimated. However, as the existing levels of service use and the impact that rivastigmine would have on this were unknown the assumed additional NHS costs were described as illustrative. These additional costs ranged from £357 over 1 year to £780 over 5 years (discounted at 6%). A number of costs relating to changes in service use, costs falling on residential care services, social services, voluntary agencies and informal caregivers could not be evaluated at the time of the report because of a lack of available information.

Costs were estimated for each of the AD severity levels in the cost-effectiveness studies. Studies by Fenn and Gray[91] and Hauber and colleagues[92] excluded costs for rivastigmine. The Canadian analysis by Hauber and colleagues[93] included the cost of rivastigmine. Studies estimated the expected annual per-patient costs for each AD severity level by combining information on the unit costs of home- or community-based care and the costs of institutional care with the probability of institutionalisation. In their estimation of health state costs, studies use various country-specific data sources for unit costs and probability of institutionalisation (see Appendix 13).

Fenn and Gray[91] in their analysis do not estimate medical costs associated with particular MMSE scores. Instead they use data from their previous study of AD costs,[126] updated to 1997 prices, to estimate the unit costs of home care and institutional care in the UK. The cost per patient-year in long-term institutional care was an estimated £18,162, in comparison with £1,899 for patients living at home. Costs of living at home included GP consultations, outpatient visits, day care, respite care, home care, meals on wheels and short-term hospitalisations. The costs of informal care were not included. The authors then used a UK survey of patients with AD in long-term care[127] in conjunction with the known distribution of non-institutionalised patients with AD from the trial to determine the likelihood of institutional care for each of the AD severity groups. In the mild AD stage they estimated the probability of institutionalisation to be 0.063, rising to 0.115 in the moderate stage and 0.459 in the severe stage of AD. The probabilities were then combined with the unit costs of home care and institutional care described above to produce weighted estimates of the annual cost of care for patients at each of the three severity levels of AD. The estimated total annual cost for a person with mild AD is reported to be £2923, with moderate AD £3770 and with severe AD £9363 (all excluding drug costs).

Cost-effectiveness of rivastigmine – summary results

Appendix 14 presents summary findings on the cost-effectiveness of rivastigmine across all included studies. Studies report cost savings (excluding drug costs, and from a mostly societal perspective) with patient benefits in terms of a delay in disease progression (using MMSE scores to define stages of disease severity). The findings from the UK cost-effectiveness studies are summarised below.

Stein[90] presents summary results as cost per QALY based on drug costs only. The analysis assumes no survival advantage. Costs but not benefits were discounted. As discussed earlier, potential benefits of rivastigmine treatment were estimated to be between 0.05 and 0.08 QALY. The cost per QALY is predicted to be £16,420 for 1 year of treatment when a benefit of 0.05 QALY is assumed, rising to £31,900 for 2 years and to £73,320 for 5 years. Increasing the assumed benefit to 0.08 QALY reduces the cost per QALY to £10,263 over 1 year, rising to £45,825 for 5 years of treatment. Stein provided separate estimates for non-drug treatment costs and reports that when these are included, QALY estimates range from £14,543 to £88,915.

Fenn and Gray[91] in their analysis do not report benefits in great detail. These results are only presented in a figure where delay in disease progression is represented by the area between two curves. Delay in disease progression was used to calculate the total cost savings associated with treatment according to disease severity and the analysis indicates that healthcare cost savings may be produced that to some extent would offset therapy costs. Two subgroups of patients were considered, those with mild AD at the start of treatment and those with moderate AD. The predicted savings were extrapolated beyond the 26-week trial period to time horizons of 1 and 2 years (savings at the later time points were not discounted). For the short 26-week trial period, cost savings per patient for the mild AD subgroup were £10 and for the moderate subgroup £48. Over a 1-year time horizon mild AD cost savings were £85 and £356 in the moderate group. Cost savings only became significant, however, when the time horizon was extended to 2 years when savings in the mild AD group were estimated to be £1227 and in the moderate AD group £777. These cost savings/analyses exclude the cost for rivastigmine (product cost not known at that time), and at today's price a 2-year drug cost for rivastigmine would be ~£1700. No sensitivity analysis was undertaken/reported.

Industry submission on cost-effectiveness of rivastigmine

In their submission to the NICE technology appraisal process, the manufacturer of rivastigmine (Novartis Pharmaceuticals) presents CEA for rivastigmine plus usual care compared with usual care alone in the UK. The submission presents findings from a model developed to estimate the cost-effectiveness of rivastigmine over a 5-year time horizon. The model uses various methods to synthesise data from numerous sources in the CEA.

In order to consider the benefit of rivastigmine on patient outcomes the model uses data from **[commercial/academic confidential information removed]** a statistical model of the natural history of AD using MMSE data[128] and a modelling/mapping process estimating utility values for AD based on MMSE scores. The model used applies data from the 5-year follow-up study to plot the progress of patients over time by MMSE category or death (dropouts are also considered in the cost-effectiveness model), when treated with rivastigmine. The model of the natural history of AD developed by Mendiondo and colleagues[128] [see the section 'Modelling AD progression over time' (p. 117)] is used to simulate the experiences of the same patient group, assuming they are not treated with rivastigmine, using the baseline patient cohort from the follow-up study. Using these methods the MMSE profile of a treated and untreated patient group are presented, as per *Table 51*. The model also included a mortality rate of 5.77% per 6-month cycle (based on a study by Martin and colleagues[129]).

As we were not able to identify the exact methodology applied **[commercial/academic confidential information removed]** to model disease progression over time for treated and non-rivastigmine treated patients over time, we are unable to offer further comment on the acceptability of the methods employed (the submitted manuscript does not report detail on methods). However, we do note that the transition probabilities for the rivastigmine-treated patients over time are from open-label, non-randomised and non-controlled trials, with results reported based on those patients continuing treatment with rivastigmine over time (i.e. non-ITT analysis).

TABLE 51 *MMSE score over time for patients in 5-year follow-up study*

[Commercial/academic confidential information removed]

In order to estimate utility values associated with MMSE scores, the authors mapped data on health status from clinical trial data to the Health Utilities Index (HUI), version 3 (HUI3). A regression function for the MMSE to utility relationship was used to estimate utility scores. The relationship was Utility = 0.0982 + 0.0298 × MMSE, and it reflects that a worsening of 1 MMSE point on average is equivalent to a reduction in utility of ~0.03 units. This mapping exercise involved a number of assumptions, a great deal of interpretation (from separate scales, e.g. ADAS-cog, PDS, CIBIC-plus), and use of data from various sources such as an earlier study in AD using the HUI3.[110] Therefore, given the range of uncertainties and opportunities for measurement error and judgment, SHTAC feel the findings should be regarded as illustrative/experimental.

The modelling approach based the probability of patients receiving institutionalised care on MMSE score following data presented by Stewart and colleagues[82] (e.g. 45% probability of being institutionalised if MMSE < 10). The cost associated with institutionalised care was taken from Netten and colleagues,[130] at £16,380 per year. The cost data for home care (average

community-based care costs) were calculated based on data presented by Stewart and colleagues[82] of community costs from a societal perspective, where 23% of these costs are assumed (cited as assumption by Stewart and colleagues) to fall on the public sector, an estimate of £3231 per year is used in the industry model (the model assumes this home care cost is unrelated to MMSE/severity scores in base-case analysis). The model uses £887 per year for rivastigmine costs and an estimate of monitoring costs (outpatient and GP visits) of £468 for base-case analysis (with variations in sensitivity analysis). Patients dropping out from treatment (during a 6-month model cycle) are allocated a 3-month drug and monitoring cost. In base-case analysis the discount rate for future costs and benefits is 3.5% per year.

Results presented in the industry submission on cost-effectiveness of rivastigmine show an incremental cost of £2121 and an incremental QALY gain of 0.0862 from rivastigmine treatment over 5 years, reflecting a cost per QALY of £24,616. The submission states that where probabilistic sensitivity analysis has been undertaken, involving all key uncertain parameters, there is a probability of over 80% that rivastigmine is considered cost-effective where the NHS is prepared to pay £30,000 per QALY. From the CEAC presented, this probability would appear to fall well below 20% where the NHS was only prepared to pay £20,000 per QALY. We discuss below some concerns over the methods used for probabilistic analysis.

In addition to probabilistic sensitivity analysis, the submission presents findings from one-way sensitivity analysis on important model parameters, and the authors report that results are insensitive to most of the parameters examined. However, there is no one-way analysis performed on the assumptions surrounding the calculation of QALY values. Where cost-effectiveness analysis assumes that the only cost considerations are drug costs and monitoring costs (at base-case assumptions) the cost per QALY is £39,563. Given that the monitoring cost for those treated with rivastigmine is one of the variables that the authors highlight as impacting on results (i.e. cost per QALY sensitive to monitoring assumptions), it seems reasonable to assume that multi-way sensitivity analysis should be undertaken. Were the analysis to assume higher cost scenarios for monitoring and that only drug and monitoring costs are relevant for cost-effectiveness, the cost per QALY would be much higher than £40,000 (indeed, much higher than £40,000 per QALY if lower QALY values were also assumed in the sensitivity analysis).

Comments on industry submission for rivastigmine

We have highlighted above some concerns over the analysis presented in the industry submission for rivastigmine (see Appendix 15 for an outline appraisal of the model). Importantly, we are concerned at the sole use of MMSE to describe AD severity, to model disease progression and to reflect QALY gains associated with disease progression. As discussed in other earlier and later parts of this report, we believe that the use of cognitive function alone to characterise and model disease progression in AD is suboptimal and is likely to misrepresent disease progression. A further related and important concern is the use of data in the model on disease progression in the rivastigmine treated cohort which is from an observational study, an open-label study, which may be subject to serious bias, and which does not reflect an ITT analysis. Treatment benefit is reflected using data from treatment responders over time, therefore in later time periods it is only those patients who continue to benefit, and who may be highly motivated, who are used in comparison with a non-rivastigmine treated cohort. The methodology used to predict disease progression over time in an indirect control/comparator group is from Mendiondo and colleagues,[128] and this is based on MMSE scores. The methodology from Mendiondo and colleagues is intuitively appealing, but it is not transparent (to us) from the published paper, or the submitted industry model. The observational data used by Mendiondo and colleagues to model disease progression are from the CEARAD database, and reflects a US patient group that may not be generalisable to the UK treatment-eligible population. Furthermore, we have not identified any other applications of this methodology as a means of validation.

The industry model is presented as a probabilistic model, yet we have concerns over some of the methods used in the model. The analysis does not cover all possible variables in the probabilistic sensitivity analysis, and for a number of parameters (i.e. probability of institutionalisation, costs for home care, monitoring costs) the model does not apply distributions around a mean parameter value; instead the model uses a number of possible mean values (from various sources/calculations) and randomly selects one of the possible mean values (see further comment below). This reflects a random 'choice' (or options) of input parameters, and reflects what would be regarded as a discrete distribution, although the choice of possible inputs may have no relation to

one another. We feel that the modeller should define a mean value with a distribution around that mean value to reflect uncertainty (where the parameter input is uncertain it may be appropriate to undertake different runs of the model with separate input scenarios). Present methods may mislead those interpreting results from the model, as it indicates a distribution around a mean has been used to capture uncertainty (in fact, the modeller is uncertain on which of four or six mean values to use).

Cost estimates used in the model for institutionalised care are from data derived and presented by Netten and colleagues,[130] and although these may reflect resource use in the sample studied by those authors, the rivastigmine model does not take into account that not all costs are met by the NHS and PSS, with many patients in an institutional setting being privately funded (or at least partially funded from private sources). Furthermore, where publicly funded patients are also in receipt of state pension payments, these will be used as a transfer payment to offset funding in an institutional setting [for further discussion of this issue, see the section 'Costing considerations in the treatment of AD' (p. 108)]. Furthermore, it would appear the different cost items are in different base year prices (institutionalisation at 2001£, drug and monitoring costs at 2003£). Of note, we did find that the estimates related to monitoring of patients on rivastigmine were fairly resource intensive, and therefore expensive, in relation to information obtained from treating physicians. The industry submission assumes all treated patients will see a GP every month and have two to four outpatient visits per year. We believe that the additional monitoring resource use associated with drug treatment is limited to two outpatient visits per year, as recommended in previous NICE guidance.

We have serious concerns over the methods used to derive a QALY value, especially as it is related to the MMSE which has been shown to have high test–retest and inter-rater variation. It would appear that the pathway from QoL data to QALY value is a rather long one, with many areas subject to uncertainty and measurement error. The methodology remains unpublished (although the submission states that the methodology was used in the NICE submission in 2000), and the validity of the approach remains uncertain.

See our adjustments to the industry model in the section 'SHTAC analysis of cost-effectiveness of donepezil, rivastigmine and galantamine using the industry models submitted to NICE' (p. 131).

Economic evaluations of galantamine

Characteristics of economic evaluations

Table 52 provides a summary of the study characteristics for the five economic evaluations reporting on the cost-effectiveness of galantamine.[95–99] Studies represent country-specific analyses for Canada, Sweden, The Netherlands, USA and the UK, with a broadly similar methodology applied across all studies. The 'headline' findings across studies are a reduction in the time patients are expected to need full-time care (FTC), together with cost savings over time (four studies), or an almost cost-neutral profile over time. Further detail on study characteristics and methods is provided in Appendix 13, with detail on study findings provided in Appendix 14.

Systematic reviews on the cost-effectiveness of galantamine

One product-specific systematic review was identified, by Lyseng-Williamson and Plosker,[107] to inform on the cost-effectiveness of galantamine; it included three published economic studies[95–97] and four published abstracts (the full publication relating to at least two of these abstracts is now available). All the included published studies are discussed in the current review. Lyseng-Williamson and Plosker[107] summarise these studies and conclude that treatment with galantamine may result in cost savings from a healthcare payer perspective as a consequence of delaying the need for FTC. From a societal perspective caregiver burden may be decreased and the length of time that patients have without severe disease may be extended. However the authors pointed out that the model had several limitations, including the use of short-term data to predict long-term outcomes, the use of a single and small study as the basis for the predictive equations used in the model and that there were only two living health states (pre-FTC and FTC) in the model which may have masked any early benefits.

Estimation of outcomes within economic evaluations (galantamine)

All published economic evaluations on galantamine use the same methodology for modelling disease progression in their estimation of the cost-effectiveness of galantamine: the Assessment of Health Economics in Alzheimer's

TABLE 52 *Characteristics of economic evaluation studies for galantamine*

Characteristic	Getsios et *al.*[95]	Garfield et *al.*[96]	Caro et *al.*[97]	Migliaccio-Walle et *al.*[98]	Ward et *al.*[99]
Publication year	2001	2002	2002	2003	2003
Country setting	Canada	Sweden	The Netherlands	USA	UK
Base year prices	1999 (Can$)	1998 (€/SEK)	1998 (NLG)	2000 (US$)	2001 (UK£)
Intervention	Galantamine 24 mg daily	Galantamine 12 mg three times daily (36 mg)	Galantamine (dose not stated in text)[a]	Galantamine 16 and 24 mg daily	Galantamine 16 and 24 mg daily
Study type	CEA model (CUA)	CEA model	CEA model (CUA)	CEA model	CEA model (CUA)
Study group – AD	Mild to moderate (subgroup of moderate AD)	Mild to moderate (subgroup of moderate AD)	Mild to moderate	Mild to moderate	Mild to moderate (subgroup of moderate AD)
Perspective	Not stated (appears to be third-party payer)	Not stated (appears to be third-party payer)	Perspective stated to be broader than that of the Dutch healthcare system[b]	Stated – third-party payer	Stated – UK NHS and PSS
Industry role	Not stated – modelling methods funded by Janssen Pharma	Research supported by Janssen Research Foundation	Research supported by Janssen Research Foundation	Co-author/funding from Janssen Pharma	Funding from Johnson and Johnson Pharmaceutical Research (Janssen)
Study base-case 'headline' predictions/findings	Reduced time in need of FTC, QALY gains and cost savings over time	Reduced time in need of FTC and cost savings over time	Reduced time in need of FTC, QALY gains and cost savings over time	Reduced time in need of FTC and cost savings over time	Reduced time in need of FTC, QALY gains, almost cost neutral position at 10 years

[a] Caro and colleagues refer to two clinical trials for resource use data: Raskind and colleagues (2000)[61] and Wilcock and colleagues (2000).[64]
[b] To include all direct formal costs, regardless of reimbursement by the healthcare authorities.

Disease (AHEAD) model developed by Caro and colleagues.[131] In line with the AHEAD model, all studies report analyses based on a short-term module covering an initial 6-month (trial) period, followed by a long-term module over a 10-year time horizon.

Assessment of Health Economics in Alzheimer's Disease (AHEAD) model

The AHEAD model rests on the concept of need for FTC, and simulates the experience of a cohort of patients across three possible health states: pre-FTC, FTC and death. The model uses patient characteristics at a given time to estimate the likelihood of disease progression over time to a level at which FTC is required. When in the pre-FTC health state, patients are assumed to live at home or in a residence that does not provide extensive care. When in FTC, patients have a requirement for a significant amount (for the greater part of the day) of paid care and supervision each day, regardless of the location of care (institution or community setting), or who provides the care; incorporating paid care received at home or elsewhere in the community in addition to care in an institutional setting. Regardless of disease progression to FTC, patients are subject to the simultaneous risk of death.

The AHEAD model determines the proportion of the patient cohort in each state over time using predictive risk/hazard equations. The predictive risk equations are based on longitudinal epidemiological data reported by Stern and colleagues,[132] and derive the time-dependent hazards of requiring FTC, and of death, according to patient characteristics present at a given time.

Stern and colleagues[132] report a prospective cohort study of 236 patients, followed up semi-annually for up to 7 years. All patients met NINCDS-ADRDA criteria for probable AD and had mild dementia at the initial visit. The study constructed prediction algorithms for two

outcomes: (1) requiring the equivalent of nursing home placement and (2) death. The prediction algorithms are based on Cox proportional hazard models. In a two-stage approach, Stern and colleagues calculated a predictor index using a set of input variables, and used the predictor index to determine the number of months in which 25, 50 and 75% of patients with any specific predictor index value are likely to require the equivalent of nursing home placement, with predictions published for index values at intervals of 0.2. The same process is undertaken for the predictive equations for death. Caro and colleagues,[131] in the development of the AHEAD model, use the methods from Stern and colleagues but undertake additional analysis to broaden the scope of the predictions, producing regression equations of a continuous nature for patients aged ≤ 73 years and for patients aged >73 years (this age divide is due to data stratification in the original publication). For further information on the statistical methods applied, see Caro and colleagues.[131]

The predictive equation for 'requiring FTC' has parameter values included in the index for age, the presence of extrapyramidal symptoms (EPS), the presence of psychotic symptoms (e.g. delusions, hallucinations), age at onset, duration of illness and cognitive score as measured by the modified MMSE (mMMS). Predictions for mortality are based on an index that consists of EPS, duration of illness, gender and mMMS score.

Stern and colleagues use selected items from the Unified Parkinson's Disease Rating Scale (UPDRS) to rate EPS:[133] hypophonia, masked faces, resting tremor, rigidity, brady/hypokinesia and posture and gait abnormalities were rated as absent, slight, mild to moderate, marked or severe (analyses focused on non-drug induced EPS).

The input parameter values in the application of the AHEAD model in the cost-effectiveness studies for galantamine are taken from the galantamine clinical trials (see below). The main instrumental variable in the predictive equations, as applied in all of the published CEAs, is the impact of galantamine on cognitive function as measured by the ADAS-cog (two studies also use the presence of psychotic symptoms[98,99]). In order to enter this measure of effect into the CEA, the ADAS-cog values had to be converted to mMMS scores (this entailed first transforming an ADAS-cog value to a MMSE score and thereafter to a mMMS score). It is the opinion of the present authors that the methodological steps required to do this introduce uncertainty, and may introduce measurement error at various stages.

The AHEAD model simulates the experiences of a cohort of patients over 10 years, following an initial treatment period of 6 months, for patients treated with galantamine, and for those same patients if they did not receive galantamine. Galantamine effectiveness is reflected in the difference in cognitive function (e.g. ADAS-cog values) and psychotic symptoms (two studies) following an initial 6-month treatment period, and no further effect is assumed. Patients treated with galantamine are assumed to remain on treatment until they require FTC.

Estimates of outcomes

In the cost-effectiveness studies described above, all studies take as a starting point for the AHEAD model the status of patients at the end of the 6-month trial period (i.e. initial 6 months of treatment). The modelling approach comprises two predictive equations, one for the prediction of requiring FTC and a second which predicts death. All published studies use the predictive equation for FTC, with two studies also including the predictive equation for death.[98,99]

Study results for outcome estimation are presented in Appendix 14. Across studies, for mild to moderate AD, a reported 9.9–15% reduction in the time patients require FTC is seen, dependent upon dose; where results are reported for the subgroup of moderate AD there is a small improvement in effectiveness over mild-to-moderate AD.

Ward and colleagues[99] report on the cost-effectiveness of galantamine in the UK, using the AHEAD model. The analysis considers differences in disease progression over time between patients treated with galantamine (16 and 24 mg doses) and the same patients if they did not receive galantamine. Effectiveness of galantamine is considered on the basis of cognitive deterioration (improvements in ADAS-cog scores) and psychotic symptoms, over the initial 6-month trial/treatment period. The authors do not present details of the findings from clinical trials on these outcome measures. The baseline patient cohorts are defined according to the characteristics of the patients in the three galantamine trials.[61,63,64] For all trial patients (n = 2193) the mean age was 75.7 years (SD 8.2), 36.8% were male, mean ADAS-cog was 27 (SD 10.6), mean MMSE was 18.7 (SD 3.8), 33.5% were deemed to have psychotic symptoms and 6.2% were deemed to have EPS. Where

patients are seen to discontinue galantamine treatment (e.g. owing to non-compliance), they are assumed to have changes in cognition and psychotic symptoms equivalent to those who had never received galantamine treatment. Ward and colleagues report analyses for mild-to-moderate AD, and two subgroups of patients: those with moderate disease only (baseline MMSE < 18), and those responding to treatment (maintained or improved ADAS-cog over 6 months).

Ward and colleagues report that treatment with galantamine at a 16-mg dose resulted in an estimated 12% reduction in the time patients required FTC, delaying the need for FTC by 2.5 months. At the 24-mg dose the estimated reduction in time patients required FTC was 15%, with a delay in the need for FTC of 3.02 months. The Ward and colleagues model assumes no survival advantage from galantamine, but considers health-related QoL. Using health state utility data from Neumann and colleagues,[110] the authors apply utilities of 0.60 and 0.34, respectively, for the health states defined as pre-FTC and FTC [see discussion of Neumann and colleagues in the section 'Health state utilities/values for AD' (p. 115)]. Over 10 years the authors estimate a mean gain of 0.06 QALY (this finding is not presented by treatment regimen, i.e. 16 or 24 mg). See the discussion of the study by Neumann and colleagues in the section referred to above.

Studies by Getsios and colleagues,[95] Garfield and colleagues,[96] and Caro and colleagues[97] define their baseline cohort according to trial participants in trials reported by Raskind and colleagues[61] and Wilcock and colleagues.[64] Migliaccio-Walle and colleagues[98] define their patient cohort using combined trial data from Raskind and colleagues and Tariot and colleagues.[63] Study methods are reported in Appendix 13 and findings for these non-UK studies, with further detail in Appendix 14.

Estimation of costs within economic evaluations (galantamine)

In line with the AHEAD model format, cost-effectiveness studies assign costs to the health states for pre-FTC and FTC. Studies estimate the monthly cost associated with pre-FTC and with FTC by location, that is, community or institutional setting. As the AHEAD model simulates disease progression over time, patients move from the pre-FTC health state, which is relatively inexpensive, to the more resource-intensive health state of FTC. The cost associated with FTC is calculated as a composite cost, with proportions assigned according to the location of care (e.g. community or institution). In the estimation of health state costs, studies use various country-specific data sources for resource use and unit costs.

Ward and colleagues[99] in their UK CEA use data from two UK national surveys (conducted by OPCS during 1985 and 1986),[134] to estimate the resource used by cognitively impaired patients residing in the community or an institutional setting. Detail on the specific resources used and subsequent cost analysis is not provided (other than in one illustrative figure for community care costs). The authors estimate the cost of providing FTC to patients in the community at £433 per month and in an institutional setting £1878 per month. The estimated monthly costs at lower levels of dependency (pre-FTC) are £238 per patient.

From the two UK national surveys Ward and colleagues assume that 48% of cognitively impaired patients requiring FTC are living in an institutional care setting. Although the authors recognise that the composition of institutional care has changed considerably since the mid-1980s, they believe that the proportion of persons in institutional care as a whole had remained constant at 48% (no justification provided). For those persons assumed to be in residential care, 42% were assumed to be in private nursing homes, 37% in private residential care for the elderly, 11% in local authority care, 8% in voluntary residential care and 2% in hospital. These estimates were based on data taken from published sources on persons with dementia.

Ward and colleagues report the expected 10-year cumulative costs per patient were £28,134 for the non-galantamine treatment cohort, £28,615 for the galantamine 16 mg/day cohort (increase of 1.7% over no treatment) and £28,806 for the galantamine 24 mg/day cohort (increase of 2.4% over no treatment). Treatment with galantamine increased annual costs for the first 3 years, with costs in subsequent years partially offset by delaying the need for FTC and with 80% of the treatment cost (galantamine cost) expected to be offset over 10 years.

For subgroup analyses, Ward and colleagues predict small cost savings over time of £228 in moderate AD (16 mg/day galantamine) and more substantial savings at £1372 (16 mg/day galantamine) in the subset of patients who

respond to galantamine (with maintained or improved cognition) after 6 months.

Cost-effectiveness of galantamine – summary results

Appendix 14 presents summary findings on the cost-effectiveness of galantamine across all included studies. Studies generally report a picture of cost savings (either full or partial) over time with patient benefits in terms of a reduction in time spent requiring FTC. A number of studies report the mean gain in QALYs over time.[95,97,99] The findings from the UK cost-effectiveness study are summarised below.

Ward and colleagues[99] in their UK CEA report costs and benefits separately, showing patient benefits as a reduction in time spent in FTC, and/or a delay in requiring FTC with an incremental 10-year cost. Ward and colleagues calculate cost-effectiveness ratios (for 16-mg galantamine treatment in mild to moderate AD), stating that the incremental cost translates to £192 per discounted month of FTC avoided, or an incremental cost per QALY of £8693 (detail on these calculations is not presented but it has been assumed that they used the undiscounted QALY value per month of pre-FTC and FTC at 0.05 and 0.0283 respectively, a difference of 0.0217 QALY, against the incremental cost of £192).

In subgroups for (1) patients with moderate AD and (2) patients who respond to galantamine treatment after 6-months, Ward and colleagues predict a scenario of cost savings together with additional benefits (reduced time in FTC). Sensitivity analysis findings state that reducing the proportion of patients needing FTC who were admitted to an institution from 48 to 40% resulted in a net cost per patient (16 mg) of £731 and a reduction to 35% resulted in a net cost per patient (16 mg) of £886. Varying the utility estimate by ±50% resulted in the estimated cost per QALY for galantamine 16 mg ranging between £5810 and £17,431. The results were reported to be non-sensitive to changes in discount rate.

Industry submission on cost-effectiveness of galantamine

In their submission to the NICE technology appraisal process, the manufacturer of galantamine (Shire Pharmaceuticals and Johnson and Johnson) presents CEA for galantamine (16 and 24 mg) plus usual care compared with usual care alone. Their methodology follows that outlined above, applying the AHEAD modelling framework developed by Caro and colleagues[131] in a UK context. The analysis and cost-effectiveness results are as detailed in the published cost-effectiveness study by Ward and colleagues,[99] although the industry submission does contain other supplementary detail on methods used and findings. See Appendix 15 for an appraisal of the modelling methodology.

The manufacturer's submission reports that the CEA predicts that the mean time to when FTC is required for patients with similar characteristics to those participating in the three clinical trials (those used to populate their economic model) is 3.2 years and that the mean survival of these patients is 5.1 years. For patients treated with galantamine 16 mg/day, the delay to FTC is 2.5 months (2.63 months non-discounted) and for galantamine at 24 mg/day the delay to FTC is 3.02 months (3.18 months non-discounted). They estimate that this is equivalent to 0.06 and 0.07 QALY, respectively (non-discounted). Total costs over time were £28,134 in the absence of galantamine treatment, £28,615 for galantamine 16 mg/day and £28,806 for 24 mg/day.

The discounted incremental cost per QALY is £8693 for galantamine 16 mg/day and £10,051 for galantamine 24 mg/day. The model predicted net savings for patients with moderate AD (MMSE < 18) and for those who showed response to treatment after 6 months. Sensitivity analysis showed that findings were sensitive to the relative cost estimates for pre-FTC and FTC health states, and the relative balance between institutional and community-based care.

Comments on industry submission for galantamine

The CEA in the industry submission for galantamine largely reflects the published literature discussed above. The model used employs the methodology of the AHEAD model by Caro and colleagues[131] (see Appendix 15 for an outline appraisal of the industry model).

The structure of the model involves only two AD states (i.e. pre-FTC and FTC) and this may be seen as a crude reflection of the natural history of AD. However, the health states used can be regarded as those of interest, and may reflect a more policy-orientated view of AD than plotting stages of disease severity that are difficult to align to policy relevant outcomes. The health states and the mechanics of progression between health states are not focused solely on cognition. The model views the differences in disease progression between galantamine treatment and non-

galantamine treatment based on inputs to the risk equations, using a measure of cognition (ADAS-cog), with differences (treatment effect) in psychotic symptoms also used to consider relative disease progression [results from trial data are converted to reflect that 10.8 and 18.7% fewer patients in the treatment cohort (mild and moderate, respectively) show presence of psychotic symptoms at the end of the 6-month trial period]. From the review of clinical effectiveness an effect on cognition (ADAS-cog) is seen, but the impact on psychotic symptoms is less certain. Two published RCTs and one unpublished RCT **[commercial/academic confidential information removed]** are reported which examine NPI,[62,63] with only one[63] of the published RCTs **[commercial/academic confidential information removed]** reporting statistically significant differences between galantamine treatment and placebo.

The 10-year time horizon used in the industry model may not reflect the true length of treatment for a typical cohort of mild to moderately severe AD patients, given the expected mortality in this elderly patient group, and the expectation that many will not be on treatment for this time period (i.e. AD will progress beyond the moderately severe stage). The industry model predicts a mean survival of around 5 years. A shorter time horizon of 5 years may be more suitable, or at least it would be expected that this time horizon would be varied in sensitivity analyses.

Cost estimates used in the model are derived from data presented by Kavanagh and colleagues[120] [discussed in the section 'Costing consideration in the treatment of AD' (p. 108)], and it is noted that these cost estimates do not take into account the fact that not all costs of care for AD are met by the NHS and PSS, with many patients in an institutional setting being privately funded (or at least partially funded from private sources). It is also noted that where publicly funded patients are in receipt of pension payments, these will be used as a transfer payment to offset funding in an institutional setting (see further discussion of these points in the section referred to above).

The AHEAD model methodology has been discussed above, and concerns have been highlighted that the data used to derive the predictive risk equations are from an observational study reported by Stern and colleagues,[132] with data on 236 patients over a period of 7 years. This methodology has been used across a number of country-specific studies to consider cost-effectiveness of galantamine, but wider use of the model methodology within the literature on AD has not been identified. This review has attempted to apply the AHEAD methodology below in a simple cost-effectiveness model for AD. The industry model uses risk equations to predict both need for FTC and death in the patient cohort, yet given the availability of mortality data in UK patients with AD, it may be more appropriate to use this data when modelling disease progression, or at least to compare the predicted mortality in the AHEAD model with published estimates. The industry model predicts cumulative death in the galantamine (16 mg) cohort and placebo cohort **[commercial/academic confidential information removed]** and this may be an underestimate of the mortality expected in the UK treatment-eligible patient group.

Examining the industry model (in Excel format), we have not been able to make a direct association between the published methodology and that employed in the model, although they are broadly similar in appearance. **[Commercial/academic confidential information removed]**

Concerns have also been highlighted that the risk equations employed in the AHEAD/industry model use mMMS as an input variable and that there is a need to transform ADAS-cog or MMSE scores to reflect an mMMS score. These transformations introduce potential for measurement error. Doraiswamy and colleagues[135] report analysis of the relationship between ADAS-cog and MMSE, reporting a highly significant correlation. The current review's examination of the relationship used to convert scores from ADAS-cog to MMSE (using published data where both outcomes are reported) indicates that it is a reasonable reflection of the two cognitive measures (although consideration of the entire continuum of possible scores was not possible). There are few reports of mMMS, therefore it has not been possible to consider the transformation of scores in a similar investigative manner. The only information on the transformation to mMMS is from the work of Stern and colleagues,[132] where a linear equation is used to estimate the mMMS from the MMSE.

The model used does not employ probabilistic methods, to enable probabilistic sensitivity analyses. The industry submission does not report sensitivity analyses.

See our adjustments to the industry model in the section 'SHTAC analysis of cost-effectiveness of

donepezil, rivastigmine and galantamine using the industry models submitted to NICE' (p. 131).

Summary of published systematic reviews that offer a broader reporting on the cost-effectiveness of donepezil, rivastigmine and galantamine

Best evidence syntheses of data on the efficacy and cost-effectiveness of donepezil and rivastigmine have been conducted by the Wessex Institute for Health Research and Development (WIHRD) in 2001 on behalf of the NHS R&D HTA programme in the UK[1,136] and by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) in 2000.[78,108,137] The studies included in the economic evaluation sections of the two reports were almost identical. The WIHRD report included five economic evaluations of donepezil[81,82,84–86] and four economic evaluations of rivastigmine.[90–93] Two unpublished reports prepared for NHS committees, one on donepezil and one on rivastigmine,[81,90] were absent from the CCOHTA report. The CCOHTA report included eight evaluations of donepezil[82–86,138,139,140] and three of rivastigmine.[91–93] Three studies on donepezil[138–140] which were included in the CCOHTA report were absent from the WIHRD report because *a priori* criteria meant that abstracts[140] were excluded and required that both costs and consequences be reported (the other two studies[138,139] reported costs only). The last two studies are also excluded from this report for the same reasons and although abstracts are included these are only briefly reported on.

The WIHRD report was conducted from the perspective of the NHS and PSS. WIHRD reported that cost-effectiveness base-case estimates in the five evaluations of donepezil all demonstrated increased effectiveness associated with cost saving in two studies but being more costly in the other three. In addition, subgroup and sensitivity analyses led to wide fluctuations in cost-effectiveness estimates which WIHRD thought cast doubt on the robustness of these estimates, particularly as some of the subgroup analyses led to conflicting results between studies. The evaluations of rivastigmine were difficult to interpret because overall effectiveness was not reported in two studies and because these studies did not include drug therapy costs. Cost-effectiveness ratios could not be extracted from these two studies.[91,92] The report concluded that there was great uncertainty surrounding the cost-effectiveness of donepezil and rivastigmine.

The CCOHTA report reviewed donepezil and rivastigmine because these were the only agents licensed for use in Canada for the treatment of mild-to-moderate AD at the time of the report. Of the seven donepezil studies considered, donepezil was the dominant strategy in three, in two was cost neutral and in the remaining two donepezil treatment was associated with increased costs coupled with increased benefits. In contrast, all the studies of rivastigmine reported cost savings. The authors of the report concluded that donepezil and rivastigmine were both associated with either a slight increase or slight decrease in overall costs coupled with a better clinical outcome for patients in the mild-to-moderate AD category. It was acknowledged, however, that gains of time in a non-severe AD state were very small even in the most optimistic of scenarios. In addition, the cost savings predicted by the models occurred primarily because of a reduction in informal care costs and delays in institutionalisation. The CCOHTA report authors felt that the former was difficult to measure and that the drugs in question had not been proved to impact significantly on the latter. Given that the models were based on short-term efficacy data rather than effectiveness data, the results could be viewed as speculative.

Economic evaluations of memantine

Characteristics of economic evaluations

Table 53 provides a summary of the study characteristics for the five economic evaluations reporting on the cost-effectiveness of memantine.[100–104] The studies represent country-specific analyses for Finland, Norway, Spain and the UK, with a broadly similar methodology applied across all studies. *Table 53* reports the 'headline' finding across studies of an improvement in time in autonomy (time spent in state defined as independent) together with cost savings over time (2 years[104] to 5 years)[100–103] (four of these studies reflect a societal perspective). Further detail on study findings from François and colleagues[103] and Jones and colleagues[104] is provided in Appendix 14, with detail on study characteristics and methods presented in Appendix 13. However, further detail on study findings, characteristics and methods is not provided for those studies available only as abstracts.

TABLE 53 *Characteristics of economic evaluation studies for memantine*

Characteristic	Guilhaume *et al.*[100]	Launois *et al.*[101]	Antonanzas *et al.*[102]	François *et al.*[103]	Jones *et al.*[104]
Publication year	2003 (abstract)	2003 (abstract/poster)	2003 (abstract)	2004	2004
Country setting	Finland	Norway	Spain	Finland	UK
Base year prices	Not stated	Not stated	Not stated	2001 (€)	2003 (UK£)
Intervention	Memantine	Memantine 20 mg	Memantine	Memantine	Memantine
Study type	CEA model	CEA model	CEA model	CEA model	CEA model
Study group – AD	Moderately severe and severe	Moderately severe and severe	Moderately severe and severe	Moderately severe and severe	Moderately severe and severe
Perspective	Stated – societal perspective	Stated – societal perspective	Stated – societal perspective	Stated – societal perspective	Not stated – appears to be NHS and PSS
Industry role	Not stated. Authorship included manufacturer	Study funded by manufacturer	Not stated. Authorship included manufacturer	Study funded by manufacturer	Study funded by manufacturer
Study base-case 'headline' predictions/findings	Improvement in time spent in independent state, and cost saving (5 years)	Improvement in time in autonomy, cost saving (5 years)	Improvement in time in autonomy, cost saving (5 years)	Improvement in time spent in independent state, cost saving (5 years)	Improvement in time spent in independent state, cost saving (2 years)

Estimation of outcomes within economic evaluations (memantine)

All of the studies use a modelling approach to consider disease progression over time. Studies report that disease progression was modelled over time (2 or 5 years) in patients with moderately severe and severe AD, based on severity level, dependency level and care setting. Data on modelling methods are limited in the published abstracts so it is not possible to offer further detail here. However, from the published abstracts it appears that all studies followed a similar disease progression modelling method to that described in the studies by François and colleagues[103] and Jones and colleagues,[104] which is described below.

François and colleagues'/Jones and colleagues' model of AD progression (memantine)

Jones and colleagues[104] report on the cost-effectiveness of memantine versus no pharmacological treatment using a Markov-type model of disease progression through health states (13 states including death) defined according to a combination of cognitive function (using MMSE score), physical dependency (either dependent or independent) and place of residency (either community or institution).

For disease severity, moderate AD is defined using an MMSE score of >14, moderately severe AD is defined as an MMSE of 10–14 and severe disease is defined as MMSE of <10. Dependency level is based on the ability to perform daily tasks as measured by the ADCS/ADL inventory modified for severe dementia.[141] Using methods developed in the post-National Dementia Economic Study (NADES), patients were classed as independent or dependent based on ADL subscores (basic and instrumental) measured using ADCS/ADL.[142] The model considered disease progression in a cohort of patients who received no pharmacological treatment and in a cohort treated with memantine, considering the differences in the context of cost-effectiveness analysis. The primary outcome of the model is 'time to dependency'; in addition the outcome of 'time to institutionalisation' is considered by both François and colleagues and Jones and colleagues, whereas QALYs are only considered by Jones and colleagues.

François and colleagues used data from a Finnish epidemiological study (the Kuopio 75+ Study[143]) to classify patients at the start of the model. In the UK study by Jones and colleagues, the initial distribution of patients by severity, dependency and institutionalisation was based on a UK epidemiological study – the LASER AD Study[146] [see the section 'Costing considerations in the treatment of AD' (p. 108) for an outline summary

of this study]. Transit probabilities covering severity, dependency and institutionalisation for the no treatment cohort were based on clinical trial data from Reisberg and colleagues (2003)[72] and data from the LASER-AD Study. Transit probabilities for dependency and location were based on a transformation of the rates from the no pharmacological treatment group using an estimated OR for memantine versus placebo, using clinical trial data. Treatment effect was applied to the first 12 months (2 × 6-month cycles), using data from the RCT by Reisberg and colleagues[72] (6 months) and an open-label follow-up study (6 months post-trial) (Reisberg B and colleagues, 2000, unpublished). Dropouts from treatment were not considered within the model.

The model uses a multiplicative probability to transit patients between states defined according to a combination of disease severity, dependency and location. Where patients are defined as institutionalised (either at the start of the model or on entering an institutionalised health state) they remain in that state, with transit probabilities applied to patients in a community setting only (either remain in community or enter institution).

The model uses Monte Carlo simulation methods in a probabilistic sensitivity analysis, (although Jones and colleagues do not present CEACs, presenting only range and best- and worst-case scenarios). Dirichlet *a priori* distributions were used to handle uncertainty associated with transition probabilities in the model.

Estimates of outcomes

François and colleagues report that patients treated with memantine showed greater duration of independence (a mean additional 4 months of independence) and time spent in the community prior to institutionalisation (approximately 1 extra month), compared with placebo patients. Outcomes are discounted at 5%.

Jones and colleagues report that based on model findings, treatment with memantine compared with no pharmacological treatment was expected to result (over 2 years) in an improvement in terms of years of independence (0.10 years, SD 0.04), an improvement in years in the community (3 additional weeks before institutionalisation, 0.06 years, SD 0.04) and 0.04 (SD 0.03) additional QALY. Outcomes are discounted at 3.5%. Health state utility values used are 0.65 (SD 0.20) for independent AD health states and 0.32 (SD 0.31) for dependent health states. These values are cited from an unpublished Danish study by Kronborg Andersen and colleagues, and the respective sample sizes for these estimates were 131 independent patients and seven dependent patients (although the authors do offer support for the dependent values from a further small sample of 18 dependent dementia patients). The data used to derive health state values are from a cross-sectional study reporting data from a Danish cohort of patients aged 65–84 living in Odense, Denmark.[145] In this study a total of 244 patients with mild to severe dementia were interviewed. Data have subsequently been mapped (by Kronborg Andersen and colleagues) across to EQ-5D health states, and values derived using Danish EQ-5D population values (tariffs). The study included 164 patients with AD, 132 of whom were living in the community, and the mean MMSE score for these AD patients was 20.6, hence the generalisability of data from these patients to the more severe patient group eligible for memantine treatment may be in question (this issue is discussed further below).

Subgroup analysis was undertaken by Jones and colleagues, where treatment groups at the start of the model were assumed to be only those classed as (a) moderately severe and independent, (b) moderately severe and dependent, (c) severe and independent and (d) severe and dependent. Outcomes for subgroups (a)–(c) were greater than in the base case, ranging from 0.17 to 0.26 additional years in an independent state, 0.06 to 0.13 additional years in the community, and between 0.07 and 0.09 QALYs. However, for patients classed as severe and dependent (d), the benefits were minimal (see Appendix 14).

Launois and colleagues (published as an abstract and poster)[101] report analyses over a 5-year period using a model similar to that described above. They compare memantine 20 mg with no pharmacotherapy and with a strategy where patients are treated with donepezil when moderately severe, followed by no pharmacotherapy once patients reach a severe state of AD. Transit probabilities for the treatment arm containing donepezil were from a published study (by Stewart and colleagues,[82] discussed in the section 'Economic evaluations of donepezil' (p. 81)]. Baseline data for the model cohort were from a Danish epidemiological study (by Kronborg Andersen and colleagues,[145] describing a distribution of patients by severity (48% moderately severe, 52% severe). The model starts by assuming that all patients were autonomous and living in the community.

Launois and colleagues report that over 5 years the time spent in autonomy for patients treated with memantine was 12% greater than for patients treated with donepezil and 24% longer for patients on no pharmacotherapy. Time to institutionalisation was 7 and 11% longer, respectively.

Estimation of costs

Jones and colleagues[104] estimated health state costs by dependency and setting: community-dependent patients £5670, community independent at £2234, institution dependent at £32,919 and institution independent at £21,102 per 6 months. Data for these cost estimates are not presented in any detail, with the authors citing the LASER-AD Study[146] as the source for resource use calculations. These costs are much higher than other published cost data for AD, especially for severe AD [see the section 'Costing considerations in the treatment of AD' (p. 108)].

Jones and colleagues report that over 2 years memantine is expected to result in a cost reduction of £1963 (SD £4504). Subgroup analysis was undertaken where treatment groups at the start of the model were assumed to be only those classed as (a) moderately severe and independent, (b) moderately severe and dependent, (c) severe and independent and (d) severe and dependent. For each category of AD patient memantine was a cost-saving strategy, except for the group of severe and dependent patients where there was an estimated additional cost of £42.

François and colleagues[103] consider costs for each level of severity and setting from a societal perspective, including community care, hospital services, informal care and institutional costs. Data were analysed, using a US resource utilisation study, to estimate cost per level of severity, setting and level of dependency (costs for mild to moderate were assumed to be the same as those for moderately severe patients). Costs reflected 2001 prices and estimates used are presented in *Table 54*. The cost for memantine (20 mg) in Finland was €3.98 per day (excluding VAT). Costs were discounted at 5% per annum. François and colleagues report that over 5 years memantine treatment was cost saving compared with no pharmacological treatment, with mean savings of €1687 per patient; however, these estimates are from a societal perspective (see Appendix 14 for sensitivity analysis).

Launois and colleagues report that over 5 years patients treated with memantine showed a cost saving of €5979 and €12,364 in total healthcare costs (societal perspective) compared with donepezil and no treatment, respectively.

Cost-effectiveness of memantine

Appendix 14 presents summary findings on the cost-effectiveness of memantine, with François and colleagues[103] and Jones and colleagues[104] reporting a picture of cost savings over time (2 years) with patient benefits in terms of improvements in time spent in an independent state, time in the community and QALYs. The findings from the UK cost-effectiveness study presented by Jones and colleagues are summarised below.

Jones and colleagues[104] report base-case analysis over 2 years that shows memantine as a dominant strategy (compared with no pharmacological treatment); treatment with memantine was associated with an improvement of 0.10 year (SD 0.04) in time spent in an independent state, a delay of 0.06 year (3 weeks) (SD 0.04) before institutionalisation, an increase of 0.04 QALY (SD 0.03) and a cost reduction of £1963 over 2 years (SD £4504).

Subgroup analyses were undertaken for four groups of patients: (a) initially moderately severe and

TABLE 54 *Summary of cost estimates used by François and colleagues[103] in analysis of cost-effectiveness of memantine (€, 2001)*

Severity	Community		Institution	
Mild–moderate	4,844		17,350	
Moderately severe	5,865		17,350	
Severe	10,380		19,291	
	Independent	**Dependent**	**Independent**	**Dependent**
Mild–moderate	4,224	6,457	14,574	24,114
Moderately severe	5,102	7,800	14,574	24,114
Severe	6,124	14,379	19,098	19,291

independent, (b) initially moderately severe and dependent, (c) initially severe and independent and (d) initially severe and dependent. In the first three of these subgroups improvements in clinical effect and cost savings were greater than the base-case analysis. In group (d), memantine was associated with an improvement of 0.02 year (7 days) in time spent in an independent state, a delay of 0.04 year (14 days) before institutionalisation, an increase of 0.01 QALY and an incremental cost of £42 over 2 years.

Sensitivity analysis is reported in relation to duration of treatment and efficacy. The worst case scenario is presented as an improvement of 0.07 year in time spent in an independent state, 0.04 year in the community, and additional 0.03 QALYs and cost savings of –£529.

Industry submission on cost-effectiveness of memantine

In their submission to the NICE technology appraisal process, the manufacturer of memantine (H. Lundbeck) presents CEA for memantine compared with usual care (no AD pharmacological treatment), and cost-effectiveness of memantine when added to the management of patients stabilised on donepezil, compared with the use of donepezil alone, in moderately severe to severe AD patients. Their submission contains CEA on memantine versus no pharmacological therapy based on the study by Jones and colleagues,[104] which is discussed above (although further detail is provided on methods and findings). Furthermore, the manufacturer's submission presents separate CEA on the comparison of memantine in combination with donepezil versus donepezil alone.

Presentation of the cost-effectiveness of memantine versus no pharmacological therapy largely follows the data presented above from the study by Jones and colleagues, although there are some small differences present in the manufacturer's submission. The submission reports results at base-case scenario as an incremental QALY gain of 0.04 and a mean cost reduction per patient of £1960, suggesting memantine as a cost-effective and cost-saving treatment. Cost savings were reported across a range of cost categories with most areas reported as having small differences (in absolute terms), yet hospitalisation and institutionalisation costs were reduced by £2530 and £1149, respectively (shifts of –7.2 and –4.5%).

Subgroup analysis for memantine versus no pharmacological therapy reported memantine as cost saving in all patient groups except those who were severe and dependent AD patients, where the mean cost per QALY was £4200 (0.01 QALY, and an additional £42). One-way sensitivity analysis on key parameters showed the effect of memantine on costs and QALYs decreased with decreasing effects on dependency, but remained in favour of memantine (additional benefits, cost savings).

Memantine in combination with donepezil, versus donepezil alone

Cost-effectiveness of memantine in combination with donepezil was estimated by the manufacturer using clinical data from the US study MEM-MD-02.[74]

[Commercial/academic confidential information removed]

Comments on industry submission for memantine

The industry submission is based on a state transition model, describing disease states by severity, dependency and location, and this is a reasonable attempt to describe disease progression in the more severely affected AD patient group, where severity alone is not sufficient to differentiate between patient groups. The time horizon of 2 years seems appropriate, with 6-monthly cycles used to fit clinical data (see Appendix 15 for an outline review of the model). However, transition probabilities used to model disease progression are from a combination of observational data and clinical trial data, with concerns over both in the context of the current UK analysis. Baseline and memantine transit probabilities for severity are from the clinical trial by Reisberg and colleagues,[72] a 6-month RCT (n = 252) (see Chapter 4). This trial reports a statistically significant difference of 2.1 points on the ADCS/ADL (functional outcomes), a non-statistically significant difference on CIBIC-plus, a statistically significant difference on scores for the SIB, no statistically significant difference on MMSE, behaviour and mood (NPI) or the GDS, yet transit probabilities show substantive differences between memantine and placebo. For example, with usual care (placebo) there is a 45.2% probability of transiting from moderately severe to severe over a 6-month cycle, whereas with memantine this probability is stated to be 22% (a difference of 23%). The power of the clinical trial to drive such differences in the disease progression model must be questioned.

Transit probabilities by dependency are cited from the LASER-AD Study[146] and the RCT from

Reisberg and colleagues.[72] These probabilities are reported in the industry submission but do not form part of the published papers. The LASER-AD Study is a 6-month observational study, funded by the manufacturer of memantine, and may be subject to bias from a number of sources such as selection bias and reporting bias. The authors of the LASER-AD Study note that it was made up of volunteers who may have been particularly motivated, and therefore unrepresentative. Transit probabilities by dependency and location from the RCT show distinct differences (between memantine and usual care), and the derivation of probabilities and their generalisability to the UK population raise some concerns. Furthermore, the validity of applying a derived OR to adjust probabilities according to memantine treatment versus usual care introduces further uncertainty, and we have concerns over the methods used to derive ORs. For example, an OR of 0.147 was calculated to adjust transition probabilities for location (probability of institutionalisation) using data on a subset (a treated per protocol subset) of patients from a clinical trial,[75] using 6-month data on institutionalisation rate (with 6/66 placebo and 1/84 memantine patients institutionalised, respectively). The industry submission cites a resource utilisation study by Wimo and colleagues[147] as the source for these data, yet SHTAC have not found these data in the published study, or in the associated published RCT by Reisberg and colleagues;[72] furthermore, rate of/time to institutionalisation is not stated as a prespecified outcome in the trial.

Cost data used in the industry submission are also from the LASER-AD study, and they seem high compared with other published data on AD. We discuss the study in outline in the section 'Costing considerations in the treatment of AD' (p. 108), but again highlight that the study is open to bias and the sample may have been unrepresentative. The cost estimates are based on a 3-month period of patient recall, which may introduce recall bias and measurement error. Furthermore, the submission does not take into account that not all costs are met by the NHS and PSS, with many patients in an institutional setting being privately funded (or at least partially funded from private sources). Furthermore, where publicly funded patients are also in receipt of pension payments, these will be used as a transfer payment to offset funding in an institutional setting (further discussion of this issue can be found in the section referred to above). The published resource utilisation study by Wimo and colleagues[147] reporting resource costs for patients in the placebo and memantine arms of the RCT by Reisberg and colleagues,[72] present estimates of US$8194 and US$7104 per month, respectively (1999$), but these estimates are from a societal perspective and contain caregiver time costs and productivity losses which account for over 90% of these cost estimates.

We have serious concerns over the use of health state utilities/values in the model for the calculation of QALYs. As stated above, health state utility values used in the industry submission are 0.65 (SD 0.20) for independent AD health states and 0.32 (SD 0.31) for dependent health states. These values are cited from an unpublished Danish study by Kronborg Andersen and colleagues, and the respective sample sizes for these estimates were 131 independent patients and seven dependent patients (although the authors do offer support for the dependent values from a further small sample of 18 dependent demential patients). The data used to derive health state values are from a cross-sectional study reporting data from a Danish cohort of patients aged 65–84 years living in Odense, Denmark.[148] In this study a total of 244 patients with mild to severe dementia were interviewed. Data have subsequently been mapped (by Kronborg Andersen and colleagues) across to EQ-5D health states and values derived using Danish EQ-5D population values (tariffs). The study included 164 patients with AD, 132 of whom were living in the community. Data on health state values are from a total group of 138 patients, whereas the authors report that 164 AD patients were interviewed, with no explanation offered on the exclusion of patients. The mean MMSE score for the 164 AD patients was 20.6. Of the 164 AD patients interviewed only 22 were classed as severe (MMSE < 10), 91 (55.5%) were classed as mild (MMSE 20–30) and 140 were classed as independent. Therefore, the majority of patients may be regarded as mild and independent, and the generalisability of data from these patients to the more severe (moderately severe to severe) patient group eligible for memantine treatment is dubious. In the initial patient distribution used for the industry model, over 70% of patients start in a dependent state, with 60% classified as severe and dependent. Supplementary data presented in the industry submission report a mean health state value of 0.486 for a sample of 12 patients with severe dementia. It also reports only a small difference between those patients in the community (n = 191) and those in an institution (n = 20), with health state values of 0.62 and 0.56, respectively.

The process of mapping from interview data to EQ-5D health state values (tariffs) introduces potential for misrepresenting the EQ-5D

classification system, the issues of 'goodness of fit', as the two health descriptions used have distinct differences. For example, (1) where the EQ-5D classifies usual activities the Odense Study refers to ability to perform 'hobbies' in the home; (2) where the EQ-5D states 'unable to wash or dress myself', the Odense Study states 'unable to wash or dress without help', and these descriptions may contain subtle, yet important, differences; (3) where patients in the Odense study refer to a poor assessment of own health status it appears that this is mapped to an EQ-5D point of extreme pain or discomfort. The use of a Danish EQ-5D tariff detracts from the generalisability of the data to a UK setting.

The source for the mortality data used in the model is cited as the LASER-AD Study[146] but the data used are not reported in the published paper; 6-monthly rates of 3.1, 7.1 and 18.8% are used in the model for mild–moderate, moderate–severe and severe AD, respectively.

The model does not include dropouts in the disease progression process, stating that this is a conservative assumption (not favouring the use of memantine) as trial data reported higher dropouts for placebo compared to memantine treatment.

Costing considerations in the treatment of AD

Identifying cost burdens

As highlighted in the earlier report to NICE,[1] the evaluation of AD treatment involves a number of different provider and funding sectors, and consideration of the various costs for treatment and who will be responsible for funding such treatment is an important issue. The primary perspective for this report (and for the NICE appraisal process) is that of the NHS and PSS, but other areas of expenditure are relevant in the overall treatment of AD. *Table 55* outlines the main sectors or components of care/funding in England and Wales for those involved in caring for people with AD.

In England and Wales, establishing the setting of care and the relevant funding source is not always straightforward, as patients and carers often contribute to the cost of care, whether institutionalised or not. For example, in the UK, patient-related private funding and social security transfer payments accounted for more than 75% of the costs for patients with advanced cognitive impairment in private households and private/voluntary residential or nursing homes (based on a 1993 report, and subsequent changes in funding affect this funding profile).[119]

AD treatment and management costs

In consideration of the costs associated with AD, the key areas, from the perspective of the NHS and PSS, are therapy costs (e.g. drug costs, monitoring) and on-going cost of care for patients by residential setting [i.e. at home, in the community and/or in an institutional setting (residential care homes and nursing homes)]. Other private patient costs and resources associated with informal carer input for AD patients are also important issues from a patient or societal perspective; however, these are not the prime focus of this report, although where possible these cost inputs are highlighted.

The expected therapeutic costs are outlined below with discussion of the literature to inform on the longer term costs for AD patients by setting of care (residential status). The focus is on the UK literature, although a large international literature is also available to inform on these issues in a broader context (e.g. see review by Bloom and colleagues[149]).

Therapeutic costs for pharmaceuticals

Product costs

Table 56 reports the cost per year for each of the drugs (by dose). These costs are based on list prices presented in the BNF (No. 49),[150] and do not include any handling or prescriptions costs, nor do they reflect any purchasing discounts which may be available for specific funding agencies.

Monitoring costs

AD patients are managed in a number of ways, either through general practice or through hospital clinics, or a combination of the two, more recently in a shared-care approach. Following discussions with treating physicians, the additional management cost for patients on drug therapy versus non-drug therapy are thought to be limited to the additional 6-monthly follow-up visits recommended by NICE in their guidance of 2000.[30] Analysis by the present reviewers included two additional outpatient appointments per year, at £108 each,[151] as an additional monitoring cost.

Literature on costs associated with treatment for AD

The literature on the cost of care for AD in the UK is not extensive. Costing studies are a combination of burden of illness studies, using aggregate data on costs and prevalence,[126,152] and

TABLE 55 *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 nurses, speech therapist, occupational therapist, physiotherapist, chiropody, clinical psychologists	NHS, SS
Drug costs (see below)	NHS, private
Community support	
Meals on wheels	SS, VO, private
Bathing/dressing (nursing)	NHS, SS, private
Home care, e.g. home help, care assistants	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 caregiver time	Private
Productivity losses	Private

LA, Local Authority; NHS, NHS via health authority or regional funding; SS, Social Services [note that the 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.
Source: Clegg and colleagues (2000).[1]

TABLE 56 *Pharmaceutical costs*

Drug	Dose (per day) (mg)	Cost per year (£)
Donepezil[a]	5	828.29
	10	1160.96
Rivastigmine	3–12	886.95
Galantamine	16	890.60
	24	1095
Memantine[a]	10	449.77
	20	899.53

[a] Cost for donepezil and memantine reduced in 2005, other products constant over 2003–05.
Source: BNF 49.[150]

survey studies often related to dementia rather than AD.[122;130] Cost estimates tend to be based on data analysis (involving assumptions) and modelling, to determine estimates of care (based on various inputs to packages of care) over time, namely annual average cost estimates.

Selected UK cost studies

Gray and Fenn[126] present findings from a costing study using a burden of illness (BOI) framework. The study uses aggregate data on relevant cost areas (hospitalisation, primary care) together with epidemiological data on AD to estimate the costs associated with AD. Estimates are based on a 'top-down' approach to the allocation of costs. The analysis, like many BOI studies, is not precise and is subject to a number of fairly broad assumptions and calculations; however, the findings are illustrative of the level of cost expected in AD, largely at an aggregate level. Gray and Fenn suggest that it costs ~£1.04 billion (1990–91 prices) to provide healthcare and social services support to people aged ≥65 years with AD in England. The study finds that most of the cost burden, around 65%, is on payments for residential and nursing home care, with a further 25% of total costs associated with hospital-based care. The BOI study presents estimates by age grouping, but does not consider cost estimates by disease severity. The estimates from Gray and Fenn were used in the cost-effectiveness study by Fenn and Gray,[91] where they are updated to 1997 prices, presenting an estimate of the cost per AD patient in long-term institutional care at £18,162, while the cost of patients in a home setting was estimated at £1899 (to include GP visits, outpatient attendance, day care and respite care, short inpatient stays and services such as meals on wheels).

Costing studies from the PSSRU have been published to inform on the costs of care for the elderly and demented patient population.[118,120,153] The PSSRU research used data from the OPCS disability survey (1985–86) to estimate the proportions of people with cognitive impairment in different types of care – private households, residential and nursing homes, and hospitals. Costs of care packages for each of these types of care were then calculated using a variety of cost sources, some dating back to the early or mid 1980s, with costs updated to 1992–93 prices. The OPCS survey included all people with dementia regardless of underlying cause; the proportion of people with AD was not recorded, and cognitive disability was measured using the OPCS SEVINT scale. Stewart[121] drew together a number of work areas,[118,120] to present cost estimates for those elderly and demented patients over 75 years old by three categories of residential setting: living alone in private household, living with others in a private household and living in residential accommodation (see *Table 57*).

TABLE 57 *Estimate of cost of care for people with dementia aged ≥75 years, by setting of care*

Care location	Estimated annual cost (1996 prices) (£)
Living alone in a private household	12,331
Living with others in private household	14,132
Residential accommodation	24,801

Source: Stewart.[121]

There remains some uncertainty over the components of cost included in the cost estimates presented by Stewart. The discussion paper states that the cost items included are direct costs of formal health and social care with informal care excluded, but data used by Stewart are from Kavanagh and colleagues,[120] which include informal care and accommodation costs.

Data from Kavanagh and colleagues,[120] which forms the basis for the cost estimates presented by Stewart,[121] are presented in *Tables 58* and *59*. It can be seen from the data that around 23% of the care costs (e.g. living alone/with others in a private household) fall on the NHS and PSS budget.

Stewart[121] has also transformed the SEVINT scores (13-point scale) onto the MMSE scale (30 points) in order to calculate cost estimates by MMSE score (category) (see *Table 60*), but not every point on the MMSE score is represented. Therefore, it is unclear how the costs for AD disease severity levels, which are each defined by a particular range of the MMSE, were derived. The cost estimates presented by Stewart were based on the proportions of patients in each category of care (with residential care subdivided by four further settings of care) and cost data for care in each location, with estimates updated to 1996 prices.

O'Shea and O'Reilly[152] present findings from a BOI study of dementia, incorporating direct, indirect, formal and informal costs. They present findings for costs across acute hospital care, psychiatric care, family care, primary and

TABLE 58 *Summary of average weekly care package costs, 1992–93 prices*

Care location	DHA (£)	FHSA (£)	SSD (£)	DSS/clients (£)	Total (£)
Living alone in private household	17.46	3.03	27.26	164.30	212.05
Living with others in private household	33.21	3.19	20.13	186.98	243.51
Local authority residential home	8.15	8.15	326.02	12.20	354.52
Private and voluntary residential home	5.30	5.30	65.72	164.19	240.51
Private and voluntary nursing home	7.77	7.77	143.52	178.64	337.70
Long-stay hospital	739.95	0.00	21.94	11.20	773.09
Living with others in private household with improved respite support	57.94	3.19	41.60	186.98	289.71
Living alone in private household with improved home care	41.52	3.03	58.61	164.30	267.46
NHS nursing home	420.95	0.00	0.00	12.20	433.15
Enhanced local authority homes provision	5.78	2.60	402.65	12.20	423.23

DHA, District Health Authority; DSS, Department of Social Services; FHSA, Family Health Service Authority; SSD, Social Services Department.
Source: Kavanagh *et al.*[120]

TABLE 59 *Average weekly costs for people living in private households, 1992–93 costs, by the funding source*

Funder	Living alone (£)	Living with others (£)
District health authority	17.46	33.21
Department of Social Services	27.26	20.13
Family Health Service Authority	3.03	3.19
DSS (Department of Social Services) clients and their families		
Informal care	49.23	69.14
Personal consumption	74.9	77.67
Accommodation costs	40.17	40.17
Total	212.05	243.51

Source: Kavanagh *et al.*[120] using OPCS data.

TABLE 60 *Cost estimates for people with dementia aged ≥ 75 years, by different levels of severity*

OPCS SEVINT	MMSE	Estimated cost per year (£)
0	26	13,826
1		16,805
2		15,828
3.5	19	15,449
4.5	18	15,767
6	17	16,385
7	16	17,071
8	14	17,859
9.5	11	17,234
10.5	8	17,407
12	1	17,809
13		20,112

Source: Stewart.[121]

community care and residential care (study related to Ireland, not England and Wales). Not all areas of cost could be estimated owing to scarcity of data, and they do not include day care services, day hospital services or drug costs. Various data sources were used in estimating costs including national data sources, survey data and dementia-specific data. The estimate for the annual cost per patient (Ireland) of residential care is £16,299, based on data from the Department of Health (1995) and case-study work published by Blackwell and colleagues.[154] The average weekly cost of residential care (across various settings) was £312. The estimate for the annual cost per patient for community care is £1054.

Wolstenholme and colleagues[122] report a retrospective analysis of a longitudinal data set for a cohort of 100 patients diagnosed with AD or

vascular dementia. The study examines the relationship between disease progression (using MMSE scores and the Barthel Index) and the cost of care. Patients were recruited to a study of behaviour in dementia.[155,156] The cohort was based in Oxfordshire, UK, and at the start of the study the patients were living at home with a carer able to give detailed information about the patient. Patients (with carer support/input) were assessed at 4-monthly intervals between 1988–89 and 1999. Assessment covered cognition, behaviour, ADL, carer information and an assessment of resource use for health, social and long-term services, including the setting of care. Subjects were classed as institutionalised when they were admitted to a hospital ward or a nursing home for permanent care. Items of resource use subject to data collection were hospitalisations, respite care, outpatient treatment, day care, home care by district nurses, community psychiatric nurses, home help, home care assistants, GP and/or practice nurse visits. Additionally, the use of special aids, adaptations, incontinence products and special dietary requirements were noted. Drug costs do not appear to have been included in the analysis, although up to 1999 treatment of AD had been largely palliative. Unit costs (1998 prices) were matched to resource use profiles and the study reports cost estimates on the basis of a fixed-effects regression model.

Wolstenholme and colleagues report the total cost per patient over the course of the study to be £66,697 (SD £60,249), based on a mean follow-up over 40 months (range 1–132). Institutional care accounted for 69% of total cost. The authors also report cost by disease severity categories defined using MMSE and by Barthel Index categories; data by MMSE score are presented in *Table 61*. Cost pattern by Barthel Index categories showed a broadly similar pattern, increasing with severity.

When examining the impact of different variables on the total costs of care, the authors report that ADL (Barthel Index scores) seemed to have a much greater impact than cognitive changes on the health and social care resources used, with a 1-point decline in MMSE associated with a £56 increase in 4-monthly costs, compared with a £586 increase in cost associated with a 1-point fall in the Barthel Index (event allowing for the shorter range in the Barthel Index). The authors also report that institutionalisation is associated with an additional 4-monthly cost of £8000. The analysis also examines the impact of variables on the time to institutionalisation, and one of the key findings of this study is that it may be inappropriate to model disease progression in dementia solely on the basis of measures of cognitive change.

Netten and colleagues[130] present cost estimates for elderly people with cognitive impairment, based on two surveys commissioned by the UK Department of Health: a longitudinal survey of publicly funded admission for those aged ≥65 years (over 2500 persons) to residential and nursing home care, and a cross-sectional survey of homes for elderly people (information on 11,900 residents). The surveys were not specific to AD or to patients with cognitive impairment, but data were available on cognitive impairment and challenging behaviour via the Minimum Data Set (MDS) framework, using the MDS Cognitive Performance Scale (CPS), a seven-point scale providing information on short-term memory loss, decision-making, communication and dependency. The MDS CPS has been shown to correspond closely to the MMSE.[157]

Netten and colleagues present findings on the weekly prices across residential care settings, with indications of differences for those severely cognitively impaired compared with all residents. Prices (1998–99 levels) did not differ greatly between privately and publicly funded settings. Nursing homes and dual-registered homes were more expensive than private and voluntary residential homes. *Table 62* presents findings from Netten and colleagues on the weekly costs in the residential settings examined.

TABLE 61 *Estimated annual cost by MMSE score, reported by Wolstenholme and colleagues[122]*

AD severity	MMSE score	Estimated annual cost (1998 prices): mean (SD) (£)
Mild	>20	8,312 (5,602)
Mild to moderate	15–20	11,643 (7,808)
Moderate	10–14	15,681 (9,509)
Severe	<10	22,267 (14,507)

TABLE 62 *Weekly prices (£) charged for residential care in England (1998–99 prices), reported by Netten and colleagues*[130]

	Private residential homes	Voluntary residential homes	Dual-registered homes	Nursing homes
All residents	247	259	322	349
Severely cognitively impaired residents	248	274	333	344

TABLE 63 *Direct and indirect 3-month costs (£) of controls and patients with AD (non-institutionalised)*

Costs	Controls	Mild AD (n = 38)	Moderate AD (n = 42)	Severe AD (n = 48)
Direct medical costs	199	1,220	3,165	3,387
Total direct non-medical costs	188	474	636	902
Indirect costs	–	4,922	6,449	9,304
Total cost	387	6,616	10,250	13,593

Costs in 1993 UK£. Costs not all related to AD.
Source: Data presented by Souêtre and colleagues.[158]

Supporting data on the weekly cost of care homes are available from the website bettercaring.co.uk, with estimates based on a sample of UK regions. Private care homes are reported to have a mean weekly cost of £280 (range £248–326) and voluntary care homes £303 per week (range £253–361). Private care homes with nursing had a mean weekly cost of £370 (range £318–481) and voluntary care homes with nursing £385 (range £313–473). These data show a range of annual costs between £14,584 and £20,039.

Netten and colleagues present information on the breakdown of people who were publicly and privately funded in residential care. In the permanent stay category there were 8194 residents classed as publicly funded with 3155 classed as privately funded. There were similar proportions of patients in these funding categories that were classed as severely cognitively impaired, 29 and 27%, respectively. This indicates that in the severely impaired group around 35% of people are privately funded. This may be an important factor, as it shows that not all residential care for severely affected AD patients will be the responsibility of the NHS and PSS budget. Netten and colleagues also present findings to show that there is a similar distribution of setting of residential care for publicly and privately funded persons (e.g. 44% of publicly funded and 38% of privately funded persons are expected to be in nursing homes), although the latter group are less likely to be residents in a local authority home.

Souêtre and colleagues[158] present findings from a UK cross-sectional multicentre study examining costs associated with different severities of AD, in non-institutionalised patients (n = 128), and matched controls (n = 56). Data were collected by interview (during 1994), across patients stratified by MMSE score into mild AD (score >18), moderate AD (score 10–18) and severe AD (score <10), with data collected on resource use for the 3 months prior to interview. The study was from a societal perspective including direct and indirect resource use, with results presented in a disaggregated manner. Outline findings are presented in *Table 63*. Direct costs typically comprised hospitalisations, institutionalisations, consultations, paramedic services and medication. Direct non-medical costs comprised community care centres, social services, home modifications/equipment and other expenses (personal expense/transport costs). Indirect costs largely comprised the time spent on the patient by the caregiver.

Souêtre and colleagues highlight some methodological concerns with the study, such as valuation of caregiver time (with continuous direct responsibility resulting in instances of caregivers reporting 12–24 hours per day with patients), but also warn that the data collection was over the summer months for some patients and that caregivers may have been absent (vacation), resulting in increased institutionalisation or hospitalisation.

Livingston and colleagues (LASER-AD Study)[146] report findings from a UK epidemiological study of 224 AD patients. The objective of this study was to validate a functional classification model of AD patients, exploring the relationship between dependency and costs of care. The authors present limited information on the methods employed to estimate cost of care. An instrument, the Client Service Receipt Inventory (CSRI), is used to assess resource use, collecting information on formal and informal services received and other aspects relevant to health. Data on resource use were collected at baseline and at 6-months, covering a 3-month recall period at each assessment, and published unit costs were applied to estimate 6-month costs, as detailed in *Table 64*. Disaggregated cost data are not presented by the authors.

The authors highlight some limitations with the study, drawing attention to the fact that the patient group were volunteers who may have been particularly motivated, and therefore unrepresentative (despite being representative in epidemiological characteristics, i.e. cognition). **[Commercial/academic confidential information removed]**

Who pays for institutional care?

In the UK, institutional care is not funded in all cases by the NHS and PSS, and there are a number of different criteria and conditions which must be fulfilled in order for the NHS and PSS to meet the payment of institutional care costs. The NHS contribution to long-term care is limited to the cost of 'registered nurse time spent providing, delegating and supervising care' (The NHS Plan 2000, Health and Social Care Act 2001). The NHS contributes to the cost of such nursing care according to three bands of care need, these being high, medium or low, which attract weekly NHS funding of £110, £70 and £35, respectively (2002 rates).[159] Financial support for institutional care from social services is means-tested,[160] therefore many residents pay for their own nursing and residential care in an institutional setting. If a person with AD has more than £19,500 in capital they will be expected to fund the full cost of their institutional fees. Once the person's capital has been reduced to below £19,500 they become eligible for help with funding from their local authority, although capital between £12,000 and £19,500 will be taken into account when assessing their contribution; capital below £12,000 is ignored. Considerations apply where a person with dementia owns their home, and it may be counted as capital.[160] Persons are expected to contribute all of their income towards the fees (half of any occupational pension will not be considered by the local authority as income, providing it is passed on to spouse/partner), apart from a personal expense allowance of £17.50 per week (these figures apply to 2003–04).[160] Where institutional care is funded by Social Services there are usually limits on their level of funding (note: no data have been identified on these).

Netten and colleagues[130] report survey data to suggest that around 38% of residents in a permanent stay institutional setting are privately funded, reporting findings for those classed as having severe cognitive impairment where ~35% of those surveyed were privately funded. Furthermore, where patients are funded publicly there will be an issue related to transfer payments, as the state pension payments (and other pension income) for residents in institutional care are redirected to cover a proportion of the costs associated with residential care. To our knowledge, the issue of 'who pays' for institutional care has not been addressed (or allowance made) in the published literature on the cost-effectiveness of treatments for AD. Given the perspective taken in the NICE health technology appraisal process (i.e. NHS and PSS), this is an important consideration.

TABLE 64 *Six-month costs and care-giving time, per level of AD disability*

	Non-dependent (£)	Non dependent – IFD[a] (£)	Dependent (£)
Total cost of care, mean (SD)	3,133 (5,770)	9,138 (13,784)	22,510 (24,570)
Caregiving time for patients in the community, mean (SD)	222 (275)	322 (290)	523 (289)

[a] Non-dependent IFD = non-dependent but with instrumental functional disability.
Source: Livingston and colleagues[146] (2003£).

Health state utilities/values for AD

A literature search was undertaken to identify data on the health-related QoL associated with AD, in terms of health state utilities/values (see search details in Appendix 3). A scarcity of data was identified to inform on this issue, which is of great importance in CEA when decision-makers are seeking summary cost-effectiveness estimates presented as cost per QALY. The focus of the QoL literature for AD is on cognitive function and not QoL *per se*.[161] Walker and colleagues[162] presented a useful review on the general issues in relation to QoL and AD; for example, dementia affects a number of individuals in addition to the patient. A further useful reference is Leon and colleagues;[163] however, this general QoL literature is not addressed in the consideration of cost-effectiveness here. The literature identified to assist with the consideration of health state utilities for AD is discussed below.

Neumann and colleagues[110] obtained health state utility weights for AD from a US cross-sectional study of 679 caregivers of AD patients, stratified by disease severity/stage using the CDR scale stages of disease. Study investigators used the combined Mark 2 and Mark 3 Health Utility Index (HUI2/HUI3) to obtain utility weights, with respondents also completing a number of other health-related QoL instruments. The HUI2/3 questionnaire is a 15-item health state classification system. The authors reported HUI2 results separately in 1999[110] (as the generic HUI3 valuations were not available at that time), and thereafter in 2000 report a comparison of the HUI2 and HUI3 utility scores.[164]

The HUI2 comprises seven health dimensions – sensation, mobility, emotion, cognition, self-care, pain, and fertility – with 4–5 levels within each dimension (fertility was not relevant within this study), presenting a total of 24,000 unique health state descriptions. The HUI3 classification system uses eight dimensions of health – vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain – with 5–6 levels in each, presenting a total of 972,000 possible unique health states. Preference measurements (utility weights) have been estimated using multiplicative multiattribute utility functions (models) derived from data from population samples in Ontario, Canada. For the HUI2, data are available based on a population sample of parents of school-aged children (n = 293). For HUI3, preference scores are from a random sample of adults in the population of Hamilton, Ontario (n = 504). The HUI questionnaire provides a description of health for the respondent (based on the HUI2 or HUI3 system), which is then allocated a health state utility based on the estimated multi-attribute utility functions derived from the Canadian sample data.[165] The valuations for HUI2 and HUI3 health states are based on the standard gamble technique for health state valuation.

Neumann[166] asked primary caregivers to complete the HUI2/HUI3 questionnaire as proxy respondents. In the HUI2, the cognition dimension is described in terms of being able to learn and remember schoolwork, because the instrument was initially developed for paediatric use. With HUI3, cognition is described in an adult context based on remembering and thinking. Interviews were conducted via telephone. Caregivers also provided information on their own health-related QoL. Responses are converted to a 'global' utility score, with HUI2 measured between 0 and 1 and HUI3 between 1 and –0.36 (the HUI3 describes a wider range of impairment). *Table 65* shows the results from Neumann and colleagues[164] for AD patients and caregivers; for both HUI2 and HUI3 proxy patient values appear

TABLE 65 *Estimates of health state utilities using the Health Utilities Index, across AD stages*

AD stage Patient/caregiver	Overall sample (n = 679)	Questionable CDR = 0.5 (n = 52)	Mild CDR = 1 (n = 194)	Moderate CDR = 2 (n = 230)	Severe CDR = 3 (n = 140)	Profound CDR = 4 (n = 50)	Terminal CDR = 5 (n = 13)
Patients: mean (SD)							
HUI2	0.53 (0.21)	0.73 (0.15)	0.69 (0.16)	0.53 (0.17)	0.38 (0.14)	0.27 (0.11)	0.14 (0.07)
HUI3	0.22 (0.26)	0.47 (0.24)	0.39 (0.24)	0.19 (0.20)	0.06 (0.17)	–0.08 (0.16)	–0.23 (0.08)
Caregivers: mean (SD)							
HUI2	0.87 (0.18)	0.88 (0.10)	0.87 (0.12)	0.86 (0.11)	0.85 (0.11)	0.91 (0.09)	0.94 (0.03)
HUI3	0.87 (0.14)	0.88 (0.12)	0.87 (0.15)	0.87 (0.14)	0.86 (0.16)	0.90 (0.10)	0.93 (0.04)

Source: Neumann and colleagues.[164]

sensitive to disease stage (and earlier reporting of data suggests responses are sensitive to setting of care),[161] yet caregiver values do not appear to be associated with disease severity. HUI3 produces considerably lower utility scores for patients. The HUI3 has a broader descriptive system and identifies more states considered worse than dead than did the HUI2.

There are limitations with the study; it is a cross-sectional study and one-time assessments can be affected by many factors present on a particular day, the HUI2 questionnaire has not been validated for use in AD,[161] responses are from proxies (caregivers) not patients, and there may be many other factors (e.g. co-morbid conditions) that influence the respondents. In general proxies tend to rate disability at a higher level (i.e. rate it as if it has a larger impact on health-related QoL) than do patients,[167] although with AD proxies are the only practical option. The sample may not be representative of the treatment population, as they were from selected sites and were required to have an active caregiver. Furthermore, the utilities are derived indirectly using a multi-attribute model based on a community sample, with responses unrelated to AD (i.e. generic health state descriptions were used).

Neumann[166] in an earlier presentation, reported health state values for AD by severity and location (community or nursing home) (*Table 66*).

Kerner and colleagues,[168] in a US study, report health state utility data from a sample of 159 patients with a diagnosis of probable or possible AD patients (and their caregivers), and 52 control patients, recruited as part of a longitudinal study on AD care-giving. This study reports data collected using the Quality of Well-being Scale (QWB). The QWB assesses QoL across levels of functioning (i.e. using descriptive scales for mobility, physical activity and social activity) and a range of symptoms. Responses to the questionnaire provide a profile which is used in conjunction with tariff values for the QWB. The QWB uses decrements in well-being (from a position of 1.0 reflecting asymptomatic/optimum function) based on weights derived from a US sample of the general population, for health states described using the three QWB descriptive scales, and additional decrements based on reported symptoms.[169] Kerner and colleagues report an overall QWB score of 0.51 (SD 0.06) for AD patients, compared with 0.74 (SD 0.12) in controls. Results are not presented by stages of disease severity (the sample was spread evenly over CDR stages of disease).

TABLE 66 *Data on AD health state values reported by Neumann[164]*

AD stage/setting	Patients	Caregivers
Mild AD		
Community	0.68	0.86
Nursing home	0.71	0.86
Moderate AD		
Community	0.54	0.86
Nursing home	0.48	0.86
Severe AD		
Community	0.37	0.86
Nursing home	0.31	0.86

Sano and colleagues,[170] in a US study, report findings from an experimental empirical study which elicited health state values for AD health state descriptions (using CDR stages 1 and 3; mild dementia and severe dementia) from both experts familiar with AD and students unfamiliar with AD. The study used the visual analogue scale (VAS) and time trade-off (TTO) health state valuation techniques. The authors report findings from expert raters for CDR1 and CDR3 states as 0.75 and 0.26, respectively, for VAS, and 0.67 and 0.31, respectively, for TTO. Student responses are reported as 0.65 and 0.30 for VAS and 0.58 and 0.29 for TTO in CDR 1 and 3, respectively.

Mortality and AD

AD is reported to be the fourth most common cause of death after heart disease, cancer and stroke and is also associated with an increased mortality rate in comparison with the general population mortality rate.[112,129,171] Studies have taken different approaches to assessing the impact that AD has on life span; some report a hazard ratio for the increased risk of death for AD patients in comparison with the mortality risk in the general population, whereas others have developed models to try to predict the expected survival time for a person with AD.

In the UK, Burns and colleagues[172] estimated standardised mortality ratios (SMRs) for AD patients in the age groups 65–75, 75–84 and >85 years, with SMRs of 5.00, 4.07, and 2.80, respectively. Combining these data with UK mortality data presents annual mortality estimates for AD at 15.4, 30.3 and 48.5% in the 65–75, 75–84 and >85 years age groups, respectively. The data from Burns and colleagues[172] are based

on a sample (n = 178) of AD patients that would be regarded as severely affected by disease, with a mean MMSE of <10.

Burns and Forstl[112] report a 3-year mortality rate of 47% (19% annualised rate) in a sample of patients with dementia of the AD type (NINCDS-ADRDA criteria), comprising both incident and prevalent cases (although no difference was found between these groups). Data were collected from 178 subjects drawn from the Maudsley and the Bethlem Royal Hospitals in East London between October 1986 and October 1988. Mean age was 80.4 years, mean age of onset was 75.2 years and mean duration of illness was 63 months, 79% were female, 41% were at home, 44% in a hospital setting and the remainder in residential care. Within this sample, 23% were placed in the possible AD category, 48% were regarded as having severe dementia (CRD scale) and 7% were classed as having mild dementia.

Martin and colleagues[129] report data on mortality in a sample of patients with dementia compared with controls matched by sex and age who did not have dementia. Patients were followed up between 1981 and 1986 (mean follow-up 36.5 months); the survival of patients with dementia at 3 years was 70% versus 84% in controls ($p < 0.001$). Data are presented by categories of dementia, i.e. senile dementia of the Alzheimer's type (SDAT) and multi-infarct dementia (MID), with data presented separately (in figures only), showing MID to have poorer mortality, but differences between MID and SDAT were not statistically significant.

US estimates of AD mortality report varied findings. A prospective study of incident AD cases[171] estimated mortality rates for men aged 70, 80 and 90 years at 11.1, 17.8 and 33.2%, respectively, somewhat higher than the rates for women at the same ages, which are 3.4, 14.1 and 32.7. A study in which cohort data (prevalent cases) was used to develop a model to predict 12-month mortality[173] reported an AD mortality rate of 14.3%, which increased to 20.9% for those who had maximum difficulty performing two or more ADLs.

Hui and colleagues[174] consider prevalent cases of AD, and report the relative risk of death for AD associated with rate of global cognitive decline. Over 4 years 354 people were evaluated annually with 17 cognitive tests that contributed to a global cognition score. The group was divided into quartiles according to rate of cognitive decline and the three upper quartiles were compared with the quartile with the least cognitive decline. The risk of death (adjusted for global cognition at baseline, age, sex, education, baseline health and baseline disability) was 4.01, 5.68 and 9.50 for quartiles 2, 3 and 4, respectively (where quartile 4 was the group with the greatest rate of cognitive decline).

Three US studies concentrated on the population in nursing homes. Lapane and colleagues[175] reported that men with AD had substantially increased mortality rate of 54% in comparison with women at 33%. Another study[176] found that 26% of people with dementia (AD made up 74% of the cases) did not survive the first 6 months in a nursing home but following those first few months estimated survival rates for 1, 2 and 3 years post-admission to a nursing home were 66, 54 and 47%, respectively. A third study of persons with advanced dementia (proportion of AD cases not reported) found that 28.3 and 35.1% of persons died within 6 months of admission to a nursing home.[177]

Modelling AD progression over time

Despite the growing literature on the epidemiology of AD and the growing cost-effectiveness literature on pharmaceutical interventions for AD, it is still not possible to identify methodology to estimate reliably disease progression to important endpoints/outcomes (e.g. onset of severe AD, institutionalisation, need for FTC). Various approaches to model disease progression over time were discussed above. A number of models[82,84–86] have used transition probabilities from clinical trials to model AD using MMSE (cognitive function) to define health states and progression to endpoints (e.g. severe disease). These methods can have uncertainties in the actual trial data used (e.g. statistical significance, generalisability) and in the overall approach to characterise disease severity, given the growing literature that indicates that cognitive function is an unreliable approach to predicting disease progression[123–125] and outcomes such as time to institutionalisation.[43,125,178] Others have used datasets and statistical techniques to model disease progression over time,[91,128,131,179] and these methods are also subject to concerns over validity and generalisability. In the datasets used to model AD progression, all have limitations, be it the use of trial-specific transition probabilities or the frailties which exist in observational data sets reporting on AD patients over time. It is unlikely that there is a satisfactory method currently available to model disease progression in AD.

Neumann and colleagues[179] use the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) database to examine the progression of disease to mild, moderate and severe stages of AD, with death included at all stages of AD progression. CERAD is a longitudinal database of 1145 dementia patients examined annually between 1986 and 1995.[180] Stage of severity of AD (mild, moderate and severe) is based on the CDR, a measure of cognitive function. Data analysis is undertaken using a Cox proportional hazards model, to estimate transition probabilities for stage-to-stage and stage-to-nursing home transitions, presenting annual rates. The transition probabilities estimated by Neumann and colleagues underscore the rapid and progressive nature of AD. They show as an example a cohort of mild community-based patients with AD, where disease progresses to the severe/nursing home stage of AD in 25.3% of patients, and results in death in 25.5% of patients over 5-years.

As expected, there was a decrease in the numbers in the CERAD cohort over time, with 1145 patients assessed on entry, 774 at year 1, dropping to 367 in year 4 and to 85 and 16 patients assessed in years 7 and 8, respectively. However, the mortality rates in the stage transition matrix appear low, with annual probabilities for death in mild, moderate and severe, at 2.1, 5.3 and 15.3%, respectively. Compared with UK all-cause mortality rates, the mild and moderate death rates would appear an underestimate of the general population mortality rates, regardless of the presence of AD or not. However, the CERAD cohort is reported as having an age distribution that is different (younger) than the expected UK AD treatment population. In CERAD 45% are aged ≥75 years, whereas in the AD2000 trial[43] in the UK over 80% of patients are aged >75 years. The CERAD data showed a varied course of disease progression in AD, with age, gender and behavioural symptoms shown to have an impact on transition probabilities, supporting a view that modelling disease progression around cognitive function is a suboptimal approach. The authors also highlight concerns over the sample sizes involved in modelling disease progression over time, commenting that the small numbers made adjusting time-dependent probabilities for age and gender difficult, and that the CERAD data did not account for the time during which patients may have had symptoms before entry to CERAD. The CERAD stage transition matrix (in various presentations) may be a helpful tool to model baseline disease progression in a cohort of AD patients, but issues over generalisability of the patient group and adjustment to transit probabilities when patients are subject to drug therapy (e.g. donepezil, rivastigmine or galantamine) are issues that would require attention in any application of the data.

Mendiondo and colleagues present an approach for the modelling of AD progression over time.[128] They use data from CERAD to model change in MMSE as a function of time in the CERAD population. The model uses MMSE alone to predict disease progression over time, with the authors arguing that the different symptoms of AD, including daily function, cognitive impairment, or global impression of severity or change, all reflect the same underlying pathological process. However, the present authors believe that the current literature highlights that cognitive function alone is not a good predictor of AD progression.[43,122–125,178] Mendiondo and colleagues use data from CERAD with MMSE scores from 719 patients followed between 6 months and 7 years (mean 2.3 years), with values of MMSE between 24 and 3 used in the statistical modelling of disease progression (MMSE) relative to time. Mendiondo and colleagues present a mathematical representation of decline in MMSE over time, with decline dependent on average MMSE score between time intervals examined. They also present findings to show that age is a significant factor in AD progression; education was seen to be a marginally significant factor. The data suggested that disease progression is more rapid when it affects younger individuals and, given the effect of education on disease progression, the authors speculate that it may be a result of a better initial performance on MMSE by those regarded as better educated (delaying diagnosis and making the course of disease apparently more rapid). Mendiondo and colleagues warn that there was considerable heterogeneity in the raw observational data used in the modelling of disease progression, with data showing variability in measurement of MMSE unrelated to disease progression, with environmental and patient factors also offering a potential to influence estimates of disease progression.

The approach presented by Caro and colleagues[131] offers an opportunity to consider disease progression across a broader description of AD than cognitive function, using patients' characteristics and other non-cognitive AD variables. The approach of Caro and colleagues (the AHEAD model) is described in some detail above, and it is adapted in an illustrative model below, yet it still remains limited given the crude

representation of disease progression (i.e. three states for pre-FTC, FTC or death), the epidemiological dataset upon which it is based (i.e. potential limitations in the data from the small number of observations at patient level and the small numbers associated with later time periods) and the statistical uncertainties inherent in the two-stage predictive risk equations that characterise the model. Mendiondo and colleagues[181] highlight concerns over the AHEAD modelling methodology, but also conclude that it may be useful in comparing costs or changes in AD progression due to different therapies.

SHTAC cost-effectiveness analysis for mild to moderately severe AD

Cost-effectiveness of donepezil, rivastigmine and galantamine

The literature on the cost-effectiveness of donepezil is based on the use of health states defined according to MMSE scores and transition probabilities between these states. The literature on the cost-effectiveness of rivastigmine is based on a hazard model predicting disease progression over time. The industry submissions to NICE for donepezil and rivastigmine use MMSE alone to define stages of disease severity, with transition probabilities and observational data respectively used to model disease progression over time on the basis of MMSE scores. All published cost-effectiveness studies for galantamine use the AHEAD model to model disease progression over time; this uses the need for FTC as an endpoint, and applies a statistical technique (predictive risk equation) to estimate the benefits from galantamine treatment. Some reservations over the use of this methodology have already been highlighted. The industry submission for galantamine also uses the AHEAD model, referring directly to the published literature, and specifically the study by Ward and colleagues[99] for estimates of the cost-effectiveness of galantamine in the UK.

Rather than replicate the modelling approaches presented in the industry submissions, which may be suboptimal, the present authors (1) provide an outline summary and review of the models submitted and (2) provide (below) some alternative cost-effectiveness results from the industry model based on alternative parameter inputs.

In addition to the review of industry models and the presentation of some alternative cost-effectiveness results from industry models, a simple disease progression model for mild to moderately severe AD to consider the cost-effectiveness of donepezil, rivastigmine and galantamine has been developed. This model, described below, is illustrative and has been developed to help consider the cost-effectiveness of these three alternative products when modelling of cost-effectiveness estimates is undertaken using similar methods (i.e. same model method applying product-specific effectiveness data on differences in ADAS-cog scores).

SHTAC model to estimate the cost-effectiveness of donepezil, rivastigmine and galantamine

Statement of problem and perspective of cost-effectiveness analysis

As stated previously, it is felt by the present authors that all currently available modelling methods in AD are suboptimal in their approach to modelling disease progression, therefore the model here is presented as 'illustrative' of the cost-effectiveness profile for donepezil, rivastigmine and galantamine. The model estimates the cost-effectiveness of pharmaceuticals plus usual care versus usual care alone in a UK context. The perspective of the cost-effectiveness analysis is that of a third-party payer, namely the NHS and PSS in England and Wales. Costs associated with patient care from the NHS and PSS are included in the analysis, together with all patient benefits.

Strategies/comparators

Descriptions of the use of pharmaceuticals in AD and the relevance of using usual care as the comparator strategy can be found in Chapter 2.

Model type and rationale for structure

A Markov-type disease progression model has been developed for mild to moderately severe AD, to consider the cost-effectiveness of pharmaceuticals for AD. The model considers the experiences of a cohort of AD patients (mild to moderately severe) over a 5-year period for the strategies of usual care alone and usual care plus pharmaceutical intervention, and compares the differences in costs and outcomes associated with the different management strategies.

The cost-effectiveness models used in the literature and the industry submissions exhibit a large degree of variation, both across and within products, in terms of the methods used to model disease progression and the endpoints used to consider patient benefits. The present model has been developed to offer an opportunity to consider the three products when a similar modelling method has been employed.

The model structure has been informed by the systematic review of the literature on the cost-effectiveness of pharmaceuticals for AD and on the available methods for modelling disease progression in AD (see discussion above) and discussion with physicians involved in the treatment of AD. The model structure used is based on the AHEAD model presented by Caro and colleagues[131] (discussed above), which has been used in the published literature to estimate the cost-effectiveness of galantamine. *Figure 19* describes the simple model structure. The approach applies the predictive risk equation from the AHEAD model to determine a monthly hazard for progression of disease to a point where patients require FTC. This hazard rate has been used in a disease progression model, together with mortality data for AD patients, to model over time the experiences of a cohort of AD patients. The cohort analysis predicts the proportion of patients that will be located in the three possible health states (pre-FTC, FTC and death) at each monthly cycle (i.e. a time horizon of 60 months). Costs and benefits have been allocated to each of these health states, and the analysis compares disease progression and subsequent costs and benefits over time to estimate the cost-effectiveness of the intervention.

The AHEAD model presented by Caro and colleagues[131] has been described above. The model is based on the progression of disease to a point where patients require FTC; where they have a requirement for a significant amount (for the greater part of the day) of paid care and supervision each day, regardless of the location of care (institution or community setting) or who provides the care. Given the concerns in the literature over the use of cognition alone to model disease progression over time, and based on discussions with physicians, it was felt that of the methods available, the use (in our modelling approach) of the AHEAD methodology and the endpoint FTC was preferable to the use of transit probabilities from trial data for health states described solely by cognitive scores (i.e. MMSE scores). The statistical techniques used by Stern and colleagues[132] and thereafter Caro and colleagues[131] to determine the predictive risk equations used in the AHEAD model are subject to a number of concerns, but the method could be used to illustrate the potential progression of AD over time to inform on the current consideration of the cost-effectiveness of interventions.

The predictive risk equation for FTC (used in the SHTAC model) has a two-stage process to calculate a monthly hazard (risk) of patients entering FTC from the starting health state of pre-FTC. A Cox proportional hazards model is used to calculate a risk index, and this has coefficients for the presence of EPS, the presence of psychotic symptoms, a young age at disease onset (i.e. <65 years of age), cognitive function (as measured

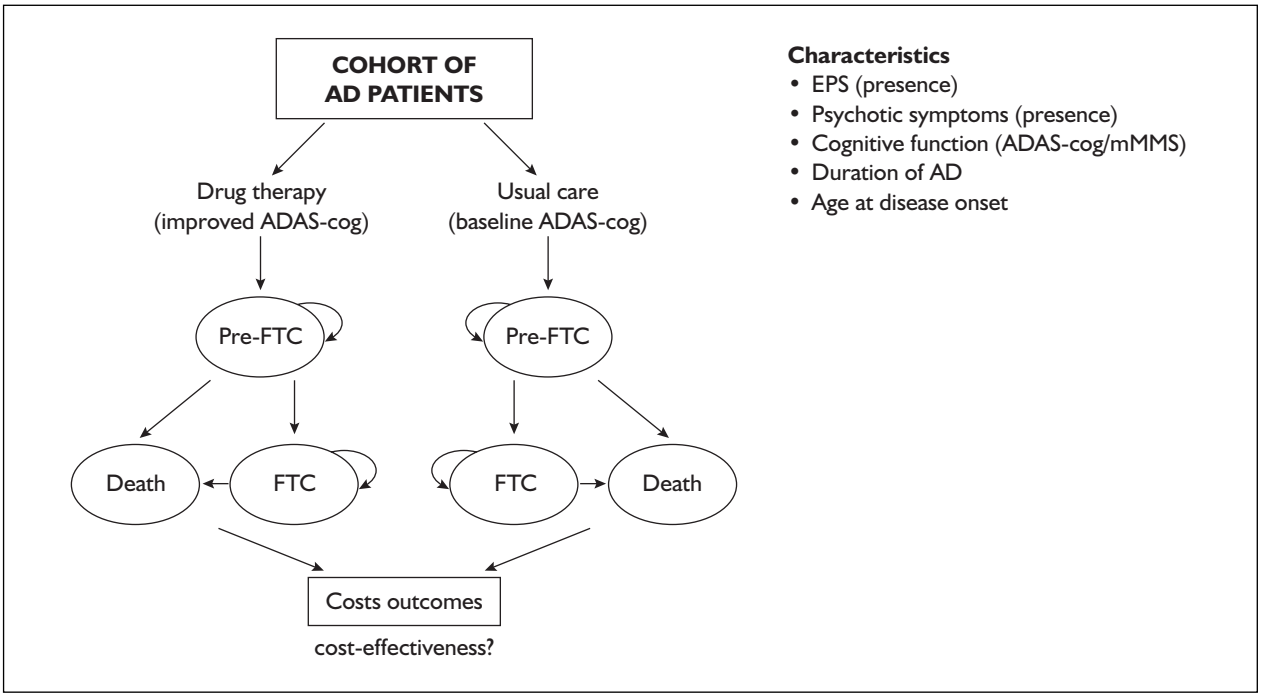

FIGURE 19 *Diagrammatic representation of SHTAC model/approach*

TABLE 67 *AHEAD model predictive risk equation for FTC*

Stage 1						
Risk index equation	**Variable**	**EPS**	**PSY**	**Young at onset**	**mMMSE**	**Duration**
	Coefficient	–0.9419	–0.4027	–0.4848	0.0724	0.0617
Stage 2						
Equations for risk over time	**Coefficient[a]**	**A**	**B**	**C**	**D**	**E**
	≤ 73 years	0.0231	–1.8117	0.0373	0.1532	–4.7903
	>73 years	0	–0.6846	0.0118	0.1413	–6.4172

[a] These coefficients have no clinical interpretation. Coefficients A–E for >73 years corrected by the present authors.
Source: Caro and colleagues.[131]
EPS, extrapyramidal symptoms; PSY, presence of psychotic symptoms.

by the modified MMSE), and duration of illness (see *Table 67*). The second stage of the process involves a regression equation to fit the functional relationship between the estimated risk index (hazard) and time. Caro and colleagues[131] present two regression models, one to predict risk over time for those aged ≤ 73 years and one for those aged >73 years (two equations owing to data limitations), with these regression equations combined with the risk index. These regression models are presented in *Table 67*.

The predictive risk equation for the need for FTC has been used to model disease progression over time, using the input for cognitive function to differentiate between the treatment strategies under consideration. That is, the risk equation is used for a baseline risk prediction, applying baseline characteristics for the cohort of AD patients, to include a measure of cognitive function (i.e. ADAS-cog score), and thereafter to predict the risks for a cohort of patients described in exactly the same way except for a change in cognitive function (i.e. ADAS-cog score) informed by the evidence on the clinical effectiveness of the intervention. Therefore, any change in the risks over time and cohort experiences could be attributed to the change in ADAS-cog score.

Patients with mild to moderately severe AD tend to be elderly (mean age ~75 years) and mortality rates tend to be high (e.g. from 11 to over 30% per year) for elderly patients with AD, so a 5-year time horizon has been used as this offers an opportunity to consider disease progression over time in AD, without extending the time frame beyond an expected treatment and/or survival period for the majority of the patient cohort. A 1-month cycle period is used in the model, as this fits with the methodology used to predict risk of disease progression to the health state of FTC. Monthly payoffs for cost and outcomes are allocated (see *Table 70*).

Baseline cohort of AD patients

Data from numerous sources to define a baseline cohort of UK patients with mild to moderately severe AD (a cohort we feel reflects the in-practice patient group) have been used (see *Table 70*). Data on mean age and ADAS-cog score are from case register and clinic data at the memory clinic of Moorgreen Hospital, Southampton. These data are reflective of reported patient characteristics in clinical trials (see Chapter 4). AD duration, from onset to diagnosis, is varied. A report from Millward Brown,[182] on diagnosis of dementia, finds an average of 32 months between onset of symptoms and diagnosis in the UK, whereas Wilkinson and colleagues[183] report a period of 12 months from onset to diagnosis. A value of 12 months is used for the AD duration parameter in the SHTAC model (with an assumed SD of 6 months), which is the conservative estimate (favouring the drug treatment cohort), undertaking sensitivity analysis at an input of 32 months. Data from the AD2000 study[43] are used to inform on the proportion of patients with psychotic symptoms (10%) and data from Stern and colleagues[132] are used for the presence of EPS (6.2%), with both of these inputs supported by data from treating physicians at the Moorgreen Hospital, Southampton.

Effectiveness data

In Chapter 4, the findings from a systematic review of the clinical effectiveness literature for pharmaceuticals for AD are reported. For the

CEA, given the limited modelling approaches for disease progression, effectiveness data on changes in cognitive function in AD are applied using findings from assessment using the ADAS-cog scale, see *Table 68* (see Chapter 4 for product-specific reporting of effectiveness, including ADAS-cog).

It is felt by the present reviewers that the above data reflect a general summary of effectiveness, as reported by ADAS-cog scores, for the three products.

Health state values/utilities

As discussed in the section 'Health state utilities/values for AD' (p. 115), the literature to inform on the health state utilities for AD is sparse and there is limited empirical evidence to inform on this model parameter. Where Ward and colleagues[99] have used the health states pre-FTC and FTC in their analysis they apply health state utility values of 0.60 and 0.34, respectively, citing the study by Neumann and colleagues.[110] This study has been discussed above, and these input values are assumed to be derived from the data presented by Neumann and colleagues by severity and setting of care (discussed in the section referred to above), adjusted for proportions in each setting. In the absence of other data these health state utility data from Neumann and colleagues, which represent a 0.26 point difference in health state values between pre-FTC and FTC, have been applied.

There is some support in the EQ-5D health state tariff methodology for such a decrement (i.e. 0.26) in health state values between the health states of pre-FTC and FTC. The tariffs are determined based on regression coefficients associated with differences in the EQ-5D classification system, with five dimensions of health across three levels of severity (of sorts). In modelling health state tariff values, the EQ-5D model is associated with an additional decrement of –0.269 when any of the dimensions are at level 3 severity. If it were to be speculated that a move from pre-FTC to FTC is associated with a move to a health state in which the person was 'unable to wash or dress self' or 'unable to perform usual activities' (with self-care and usual activities the most likely EQ-5D dimensions to be of interest at this stage of disease progression), then it would seem reasonable to consider (in terms of the EQ-5D health states tariffs) that a difference in the health state value may be in the region of –0.269. Further decrements in value would be associated with a move from level 2 to level 3 severity within the specific dimension (i.e. usual activities at –0.058, or self-care at –0.11). *Table 69* presents some hypothetical health state descriptions and tariff values to illustrate the point made here.

TABLE 68 *Effectiveness data, scenarios used in the model*

Product	Mean reduction in ADAS-cog (95% CI)	SE
Donepezil 10 mg	–3.01 (–3.91 to –2.10)	0.46
Rivastigmine 6–12 mg	–3.08 (–3.78 to –2.38)	0.36
Galantamine 24 mg	–3.28 (–3.89 to –2.67)	0.31

SE, standard error.
From SHTAC clinical-effectiveness meta-analysis (see Chapter 4).

TABLE 69 *Examples of how the EQ-5D may predict health state values for states of pre-FTC and FTC*

EQ-5D health state description	Pre-FTC (e.g. state 22222)	FTC (e.g. state 23222)	FTC (e.g. state 22322)
Mobility	Some problems	Some problems	Some problems
Self-care	Some problems	Unable to wash or dress self	Some problems
Usual activity	Some problems	Some problems	Unable to perform usual activities
Pain/discomfort	Moderate	Moderate	Moderate
Anxiety	Moderate	Moderate	Moderate
Tariff value	0.516	0.137	0.189

Source: Williams, 1995.[184]

Mortality data

Within a model of disease progression for AD, it is important to account for mortality over time, especially as the patient group is elderly and mortality rates for the elderly with AD are very high. It is likely that a large number of patients will die over a period of 5 years.[122] The life expectancy for patients with AD, from onset of disease, is thought to be around a mean of 6 years (SD 3.5 years).[171] The time from onset to diagnosis and treatment is thought to be between 1 and 4 years.

In the present analysis, a common mortality rate for all patients is used. Although it is accepted that there may be differences in mortality by age (as shown by Burns and colleagues[172]) and severity, the data do not allow us to differentiate by these groups at present. An annual mortality rate of 11.2% is applied in the model (using a monthly rate in each cycle), using data from Martin and colleagues,[129] who report a mortality rate of 30% over 3 years. Sensitivity analysis on the mortality rate used is undertaken/reported.

Discounting of future costs and benefits

A discount rate of 1.5% has been applied to future benefits and 6% to future costs. This approach is the current convention in UK CEA and is in line with the current guidance from NICE. Other discount rates have been applied in sensitivity analysis (0 and 3.5%).

Cost data

Drug costs

Patients in the treatment cohort are assumed to have been on drug therapy for 6 months prior to the start of the disease progression model, in order to accrue effectiveness (improvement on ADAS-cog) from treatment. Therefore, they begin the model with an entry cost associated with a 6-month drug cost. Thereafter, the estimated annual cost for drugs is used (as in *Table 56*) to derive a 1-month model cycle cost.

Monitoring costs

Patients in the treatment cohort are assumed to have been on drug therapy for 6 months prior to the start of the disease progression model, hence they begin the modelling process with an entry cost associated with a 6-month monitoring cost. Thereafter, the estimated annual cost for monitoring (see *Table 70*) is used to derive a 1-month (cycle) cost for monitoring. The monitoring cost reflects an additional cost, over and above usual care (covering two additional outpatient visits), and no allowance is made in our model for the ongoing management costs for the patient cohort on usual care alone.

Costs for pre-FTC

As discussed above, there is a scarcity of good-quality information on the costs for AD patients treated in the community. An estimated cost of £3937 per year for those patients living in the health state pre-FTC has been made. This estimate is based on data from Stewart,[121] and Kavanagh and colleagues[120] [see the section 'Costing considerations in the treatment of AD' (p. 108)], who present overall cost estimates, reporting that 23% of the overall cost of care falls on the NHS and PSS budget holder.

Costs for FTC

The cost for FTC has been estimated using the methods described in *Table 71*, using data from numerous sources. Cost estimates for the health state FTC comprise a proportion of patients in the health state FTC who are resident in the community (e.g. own homes) and a proportion who are resident in an institutional setting. In estimating the composite cost for FTC, it is assumed that 48% of those requiring FTC will be in an institutional setting (base-case analysis). This estimate is based on data used in studies by Ward and colleagues[99] and Stewart and colleagues,[82] with further support for this estimate available from Fenn and Gray,[91] who report a probability of institutionalisation in severe AD at 45.9%. Sensitivity analysis on this parameter value is undertaken (see below).

The estimate for costs related to FTC in a community setting is £5196 per year, based on data from the study by Ward and colleagues,[99] where resource use data are from OPCS Surveys[185] (see Appendix 16).

For costs associated with FTC in an institutional setting, importantly it is believed that not all institutional costs for AD patients will fall on the NHS and PSS budget. This has been discussed above, and an estimate of 30% for the proportion of patients who are self-funding when in institutional care (based on findings from Netten and colleagues[130]) has been used.

The estimate for FTC used in the SHTAC analysis comprises (a) institutional care at £18,471 per year, plus (b) the cost to the NHS and PSS of caring for these institutionalised patients (over and above the institutional costs) at £4874 per year; this estimate is based on resource use data (for elderly with cognitive disability) from OPCS

TABLE 70 *Key inputs to SHTAC AD model*

Model input/variable	Input value	Detail/comment	Source
Cohort characteristics			
Age (years): mean (SD)	74 (6)	Normal distribution	Clinical opinion[a]
AD duration (years): mean (SD)	1 (0.5)	Gamma distribution	Wilkinson *et al*.[183 b]
ADAS-cog: mean (SD)	24 (9)	Gamma distribution	AD2000[43]
Presence of EPS (%)	6.2	Mean	Stern *et al*.[132 c]
Presence of psychotic symptoms (%)	10	Mean	AD2000[43]
Effectiveness of drug	See *Table 68*	Gamma distribution (mean, SE)	SHTAC clinical review, see Chapter 4
Drug cost	See *Table 56*	By product/mean	BNF (49)
Monitoring cost	£108 (SD 25) per visit	2 outpatient visits Gamma distribution	NHS Reference Costs[151]
Cost for pre-FTC	£328 per month (assume SD £164)	£3,937 per year Gamma distribution	Stewart,[121] Kavanagh *et al*.[120]
Cost for FTC	£937.30 per month (assume SD of £468)	£11,247 per year, where 70% of patients are publicly funded, and 52% of FTC is community FTC[d] Gamma distribution	SHTAC estimate (see above)
Mortality rate	11.2% per year	Mean	Martin *et al*.[129]
Health state utilities			
Pre-FTC: mean (SD)	0.60 (0.12)	Gamma distribution	Neumann *et al*.[166b]
FTC: mean (SD)	0.34 (0.068)	Gamma distribution	
Discount rates			
Future costs	1.5% per year	Fixed rate	By UK convention,
Future benefits	6.0% per year	Fixed rate	NICE guidance

Costs are in 2002–03 £s.
[a] Data from Memory Assessment Research Centre, Moorgreen Hospital, Southampton, Hampshire (supported by a wide range of clinical trial data, see Chapter 4).
[b] Assumption on SD by SHTAC.
[c] Data from Memory Assessment Research Centre, Moorgreen Hospital, Southampton, Hampshire, indicate that this is likely to be less than 10% in a UK treatment group.
[d] Where all patients publicly funded and all institutionalised, estimate of mean cost per month is ~£1970 per month.

Surveys reported by Kavanagh and Knapp[185,186] (Appendix 17, **[commercial/academic confidential information removed]**) An estimate of £11,247 per year for the mean expected cost for those patients in FTC is used.

Presentation of results

Findings are reported on the mean incremental gain in QALYs and mean incremental cost per treated patient, based on a cohort analysis of 1000 patients (trial) and a simulation of 1000 trials. The incremental cost per QALY is estimated. Findings are presented using the cost-effectiveness plane, showing incremental costs and QALYs. Using the mean incremental benefits and cost per trial, the 'net benefit' associated with treatment is estimated, and a CEAC is plotted, showing the probability of a positive net benefit based on a range of threshold values for the willingness to pay per QALY.

Findings are also presented on the mean difference in time spent in FTC over the 5 years and figures are presented to show the expected

TABLE 71 *Estimate of annual NHS and PSS cost for persons in health state FTC*

	FTC in community	FTC in institutional setting		Total expected annual cost for FTC
		Institutional costs	Other NHS/PSS costs	
Annual cost (£)	5,196	18,471	4,874	
Proportion publicly funded (%)	All	70	All	
Proportion of FTC patients by setting (%)	52	48	48	
Cost (£)	2,702	6,206	2,339	11,247

Source: FTC in community and proportion of FTC in community from Ward *et al.*,[99] institutional living costs and proportion publicly funded from Netten *et al.*,[130] other NHS/PSS costs for institutionalised patients from Ward *et al.*[99] All costs uprated to 2002–03 costs (Hospital and Community Health Services index).

TABLE 72 *SHTAC cost-effectiveness results (donepezil, rivastigmine, galantamine)*

Product	Difference/reduction in time spent in FTC (months), over 5 years (non-discounted)	Incremental cost (£)	Incremental QALY	Cost per QALY (£)
Deterministic results				
Donepezil 10 mg	1.59 (1.71)	2,894.81	0.036	80,941
Rivastigmine 6–12 mg	1.63 (1.75)	2,121.18	0.037	57,985
Galantamine 24 mg	1.73 (1.86)	2,647.58	0.039	68,042
Probabilistic results				
Donepezil 10 mg	1.42 (1.53)	3,084.83	0.032	96,757
Rivastigmine 6–12 mg	1.43 (1.54)	2,302.75	0.033	70,438
Galantamine 24 mg	1.54 (1.66)	2,862.55	0.035	81,910

proportion of the drug treatment and usual care cohorts in health states pre-FTC and FTC over time.

Assessment of uncertainty in the SHTAC analysis

Sensitivity analysis was undertaken to address uncertainty in the CEA. Methodological and structural uncertainty is considered by addressing assumptions on proportions of institutional costs met by the NHS and PSS, proportions of patients in FTC by location and assumptions on monitoring.

Parameter uncertainty has been considered, where possible, as part of the probabilistic modelling process, with distributions around point estimates allowing variation within the main analysis (e.g. age, ADAS-cog score, AD duration, effectiveness, monitoring costs, costs for pre-FTC and FTC and health state utilities), but this has not been possible in all instances. Therefore, where parameter values have not been varied in a probabilistic manner, sensitivity analysis has been undertaken on these parameters by re-running probabilistic analysis with different point estimates (e.g. mortality rates, presence of EPS and psychotic symptoms). Further analyses have been run for variations in parameter variations for health state utilities and effectiveness estimates (assuming similar distributions).

SHTAC cost-effectiveness results (donepezil, rivastigmine, galantamine)

The mean survival time in the SHTAC model is 45 months (41.8 discounted months) and the mean time on drug treatment is 27.8 months (across all three products). *Table 72* presents ICERs, cost per QALY, for drug treatment plus usual care versus usual care alone. Results are presented for deterministic analysis and probabilistic analysis. For deterministic analysis the estimated cost per QALY ranges from £57,985 (rivastigmine 6–12 mg) to £80,941 (donepezil 10 mg). Findings using probabilistic analysis show a higher cost per QALY, ranging from £70,438 (rivastigmine 6–12 mg) to £96,757 (donepezil 10 mg). The incremental QALY gains over the 5-year period are small and the cost per QALY estimate is sensitive to small changes in the

TABLE 73 *Profile of mean estimated 5-year cost related to AD progression, by treatment option*

Treatment	Mean drug cost (£)	Mean increment monitoring most (£)	Mean cost for pre-FTC (£)	Mean cost for FTC (£)
Deterministic analysis				
Usual care	None	None	8,408	14,180
Donepezil 10 mg	3,445	596	8,895	12,788
Rivastigmine 6–12 mg	2,450	597	8,907	12,756
Galantamine 24 mg	3,033	598	8,938	12,666
Mean difference; usual care versus drug treatment	+2,976	+597	+505	–1,443
Probabilistic analysis				
Usual care	None	None	8,738	13,175
Donepezil 10 mg	3,271	610	9,238	12,012
Rivastigmine 6–12 mg	2,518	611	9,247	12,048
Galantamine 24 mg	3,103	608	9,258	11,706
Mean difference; usual care versus drug treatment	3,041	610	453	–1,277

incremental cost. The difference in time spent in the health state FTC over the 5-year period ranges from 1.42 months (donepezil) to 1.73 months (galantamine 24 mg), across all analyses.

Deterministic results do not include a measure of uncertainty for input parameters (e.g. costs, utilities), and importantly do not include any variation in the risk profile of the patient group (assuming the typical patient has a risk profile reflective of an ADAS-cog score at 24), therefore the probabilistic results are likely to be the more useful of the cost-effectiveness results presented here.

Table 73 presents the mean estimated 5-year costs associated with the intervention and costs associated with long-term care. The intervention does offer a potential reduction in the costs associated with FTC but these potential cost savings do not compensate for the additional drug and monitoring costs.

Figure 20 presents data from the SHTAC probabilistic analysis (base case) on the incremental costs and benefits across simulations, using the cost-effectiveness plane (plotting incremental cost and incremental benefits from simulations). The figure shows the simulations for

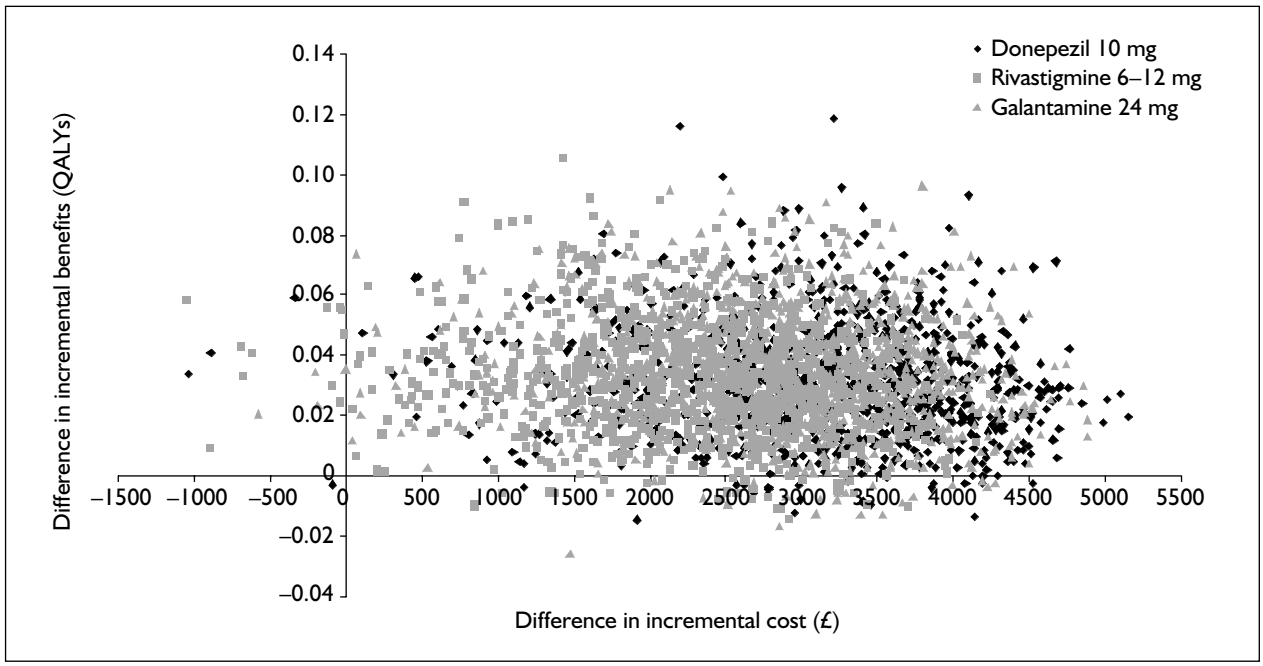

FIGURE 20 *Cost-effectiveness planes for donepezil, rivastigmine and galantamine, showing incremental costs and benefits from SHTAC model analysis (base case)*

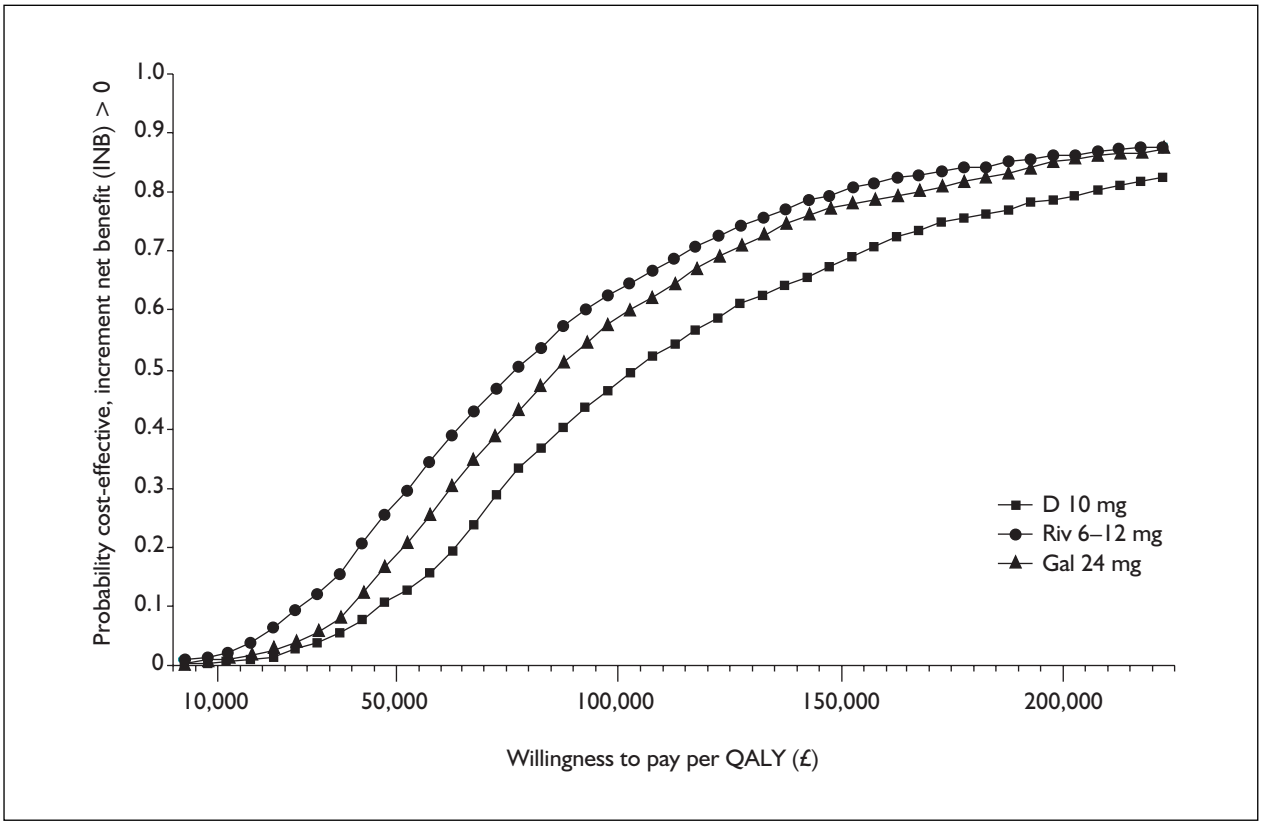

FIGURE 21 *Cost-effectiveness acceptability curve for donepezil, rivastigmine, galantamine compared with usual care alone*

all three products, with most of the observations being in the quadrant related to incremental costs and incremental benefits, and placed in the section of the quadrant which shows benefits between 0 and 0.05 QALY and costs between £1000 and £4000.

Figure 21 presents a measure of uncertainty around cost-effectiveness estimates, using CEACs, calculated using the 'net-benefit statistic' against a range of potential values representing the willingness of the NHS to pay per QALY gained. The figure shows that where the NHS are willing to pay £20,000 per QALY there is a probability of <7% that the intervention would be cost-effective. Where the NHS are prepared to pay £50,000 per QALY there is a probability of <30% that the intervention would be cost-effective, and at £100,000 the probability that the intervention is cost-effective is between 49 and 66%.

Figures 22 and *23* present data from the model to illustrate the progression of AD over time across the health states of pre-FTC and FTC (the third health state is death). The figures show a steady progression of disease over time from pre-FTC to FTC, with 46% of the usual care (placebo) cohort in FTC at 60 months and between 43.1 and 43.5% of patients from the drug-treatment cohorts in FTC at 60 months. The figures show only a small absolute difference in the disease progression profiles for no drug treatment and the three drug treatment options. Death, which makes up the missing proportion of patients, is the same across all comparators, with all patients regardless of location and treatment subject to the same mortality risk over time. With resource use in the patient groups (and by health state) being high, it only requires a small difference in disease progression to reflect an incremental cost and/or benefit (given base-case assumptions). Appendix 16 presents similar data showing predicted disease progression where there is no mortality effect included in the SHTAC model. These results show a stark difference in the location of a potential cohort of patients, and indicate that mortality is an important issue when attempting to model the expected experiences of a patient cohort with AD.

SHTAC sensitivity analyses

The results presented for probabilistic analysis have been estimated using probabilistic sensitivity analysis with a number of input variables subject

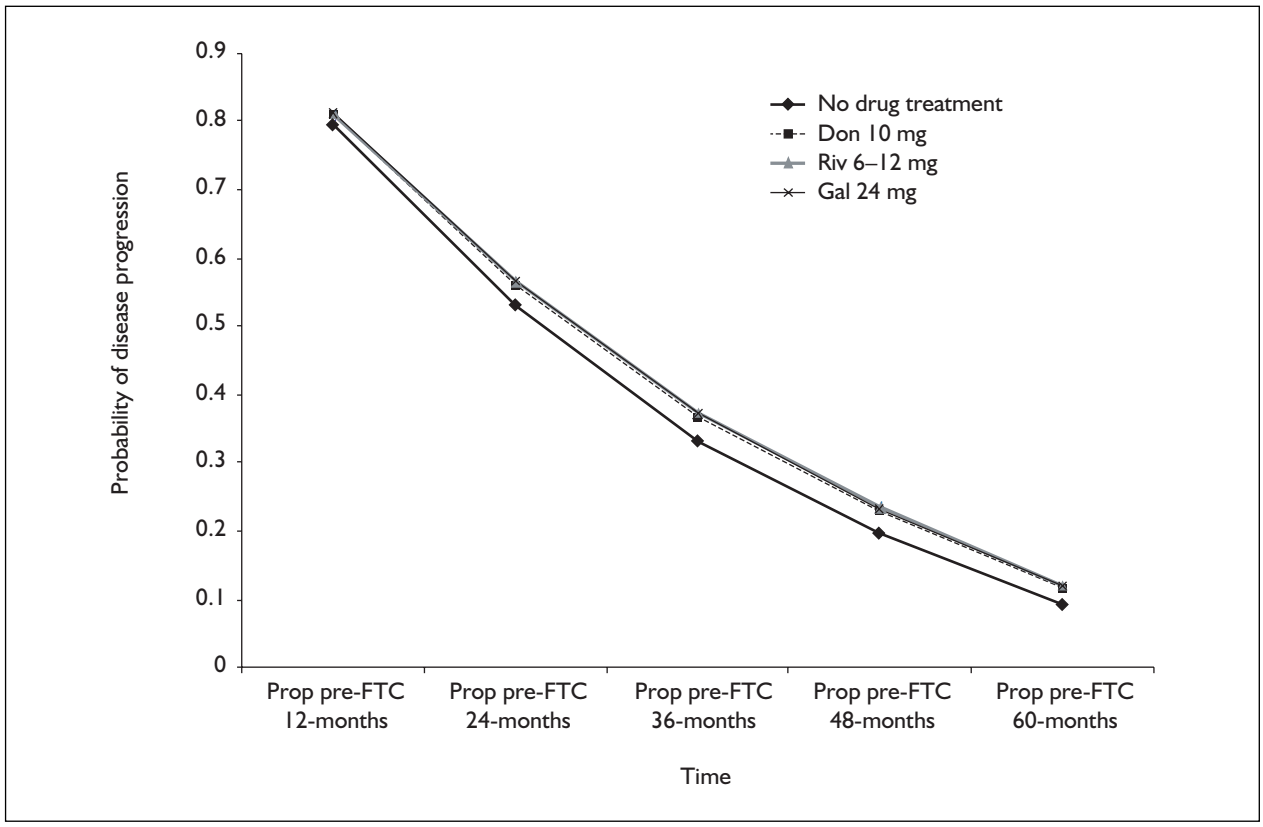

FIGURE 22 *Projected proportion of patients remaining in pre-FTC over years 1–5, SHTAC model*

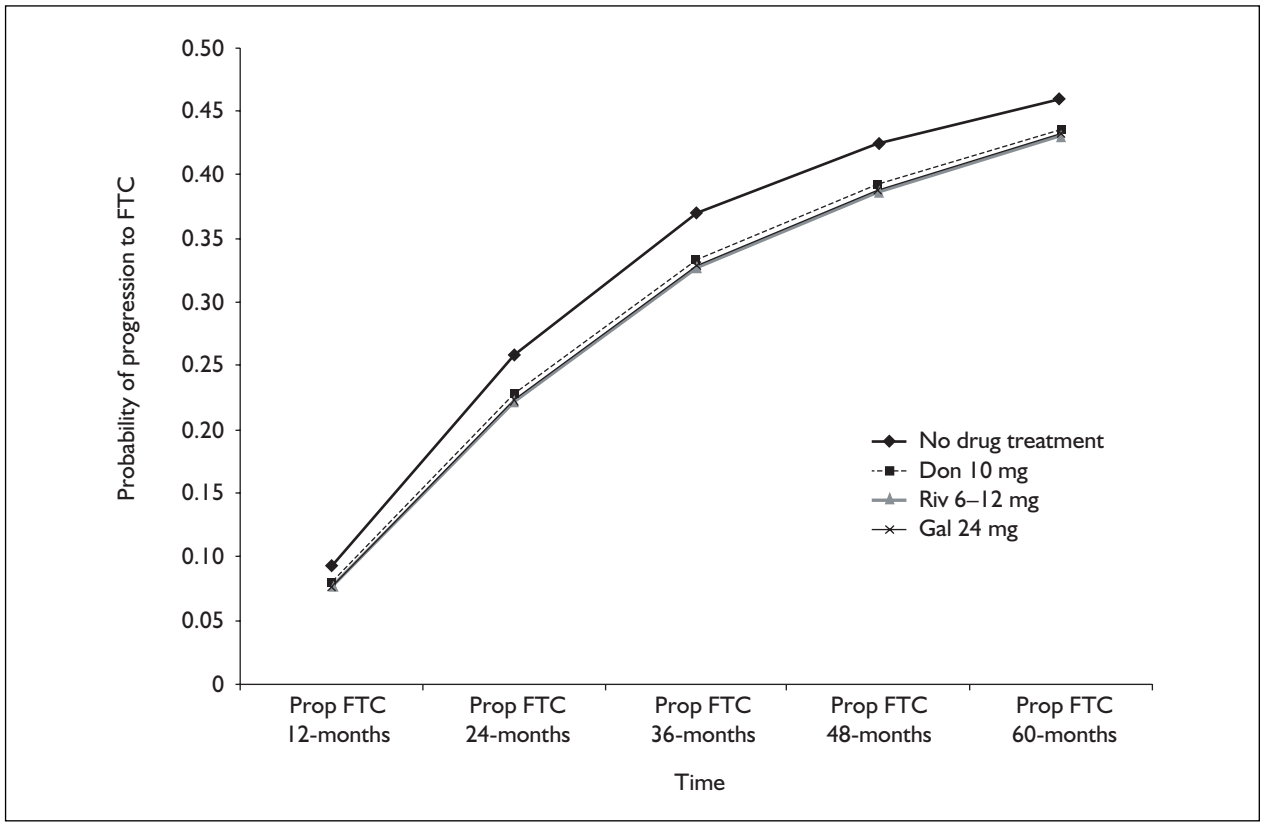

FIGURE 23 *Projected proportion of patients progressing to FTC over years 1–5, SHTAC model*

TABLE 74 *Sensitivity analysis, against probabilistic results, selected one-way and multiple sensitivity analysis using the above model with parameter/input variations*

Results of sensitivity/inputs	Cost per QALY (£)		
	Donepezil 10 mg	**Rivastigmine 6–12 mg**	**Galantamine 24 mg**
Base case	96,797	70,438	81,910
No discounting	97,751	73,692	82,246
Discount rates at 3.5% for future costs and outcomes	104,184	76,492	84,651
Assume all institutional costs met by NHS and PSS	87,096	62,269	71,971
Assume 85% of institutional costs met by NHS and PSS	94,847	65,851	76,843
Assume presence of EPS and psychotic symptoms in 20% of cohort	85,973	63,262	74,994
Assume a benefit of treatment on psychotic symptoms: with 20% reduction in the proportion of patients showing presence of symptoms:			
Base case (10% with symptoms)	94,839	68,117	78,145
20% with psychotic symptoms	84,389	58,652	71,722
75% with psychotic symptoms	56,039	37,996	48,816
AD duration (mean):			
2.66 years (SD 1 year)	103,106	76,288	87,056
Assumptions on location of FTC:			
20% community, 80% institution	84,495	57,424	71,513
60% community, 40% institution	95,217	74,414	84,632
Assume no entry cost (drug/monitoring) for treatment cohort	70,886	53,780	63,103
Assume all costs met by NHS and 80% of FTC patients in an institutional setting	69,428	40,061	50,868
Assume additional healthcare costs for institutional patients at (per year):			
£1000	105,069	73,780	86,549
£10,000	92,140	62,923	76,208
Assume costs for pre-FTC are (per month/cycle):			
£150 (SD £75)	92,287	60,376	75,020
£600 (SD £300)	109,446	82,479	95,595
Assumptions on health state utilities:			
Pre-FTC 0.75, FTC 0.20 (diff. 0.55)	45,275	33,552	38,456
Pre-FTC 0.50, FTC 0.20 (diff. 0.30)	84,576	59,975	69,919
Pre-FTC 0.50, FTC 0.34 (diff. 0.16)	161,360	111,418	136,980
Effectiveness estimate:			
+1 point on base-case ADAS-cog	66,505	49,065	57,119
–1 point on base-case ADAS-cog	150,214	120,915	122,571
Mortality at (per year):			
0%	76,365	54,103	61,477
8% – all patients	91,113	65,843	77,498
15.4% – all patients	108,125	76,662	91,603
Assume all costs met by NHS, 80% of FTC patients in institution, and mortality annual rate of 8% (all patients)	62,564	35,885	44,822
Assume additional (to base case) monitoring cost:			
+1 additional outpatient visit per year	103,411	81,080	87,753
+1 outpatient appointment, and an additional 2 GP visits per year[a]	110,898	83,541	99,162

[a] GP visit assumed to cost £26 (assume SD of £13); PSSRU.

to stochastic data input, to address uncertainty in parameter inputs (as detailed in *Table 71*). *Table 74* reports selected one-way and multi-way sensitivity analysis to address uncertainty in other parameter inputs, and in structural/methodological uncertainty.

Deterministic analyses are also presented, and sensitivity analysis for deterministic analysis reported in Appendix 18, with relative differences showing a similar sensitivity of results to those presented below.

Results are sensitive to a range of alternative inputs, particularly in relation to effectiveness, health state utility data and cost inputs for longer term care. Large differences in cost per QALY are seen where a 1-point shift (in both directions) for effectiveness data (change in ADAS-cog) is considered. Given that the benefit of the intervention is seen as delaying the time to FTC (or reducing time in FTC), results are sensitive to changes in the assumptions/costs associated with FTC, that is, where it is assumed that all institutional costs fall on the NHS and PSS and that the majority of patients requiring FTC are institutionalised, the cost per QALY is in the region of £50,000–69,000.

Where the impact of mortality, including a zero rate, is reduced, there is an impact on cost-effectiveness results but the differences are not dramatic, and the cost per QALY remains in the region of £61,000–76,000.

Owing to relatively small incremental QALY gains, the cost per QALY is sensitive to small changes in the 5-year costs; for example, where the entry costs (6-month drug and monitoring cost associated with treatment) are disregarded the cost per QALY falls to between £63,000 and £71,000, a drop in the region of £20,000 per QALY. This point is supported (in the other direction) by the increases seen in the cost per QALY estimates when it is assumed that monitoring costs are increased by one further additional outpatient appointment per year, or by one additional outpatient and two additional GP visits per year, with cost per QALY increases of around 10 and 20%, respectively.

The cost-effectiveness findings are sensitive to changes in the difference in health state values between the health states of pre-FTC and FTC. The base case shows a mean difference of 0.26 (on the 0–1 QALY scale), and with (1) an assumption of a 0.55 mean difference it is seen that the cost per QALY estimates fall by over 50%, (2) an assumption of a 0.16 mean difference it is seen that the cost per QALY estimates increase by over 50%.

Where the patient group is assumed to have a higher prevalence of EPS and psychotic symptoms (20% versus a baseline of 6.2 and 10%, respectively), small changes in the cost-effectiveness findings are seen. Where we assume a benefit of treatment on the presence of psychotic symptoms (a 20% reduction in the number of patients showing psychotic symptoms), this does have an effect on the cost-effectiveness, with the cost per QALY falling; however, only where it is assumed that the majority of the patient group have psychotic symptoms and that the drug treatment has an effect on the prevalence of symptoms does the cost-effectiveness fall dramatically.

Limitations of the SHTAC cost-effectiveness model

The rationale for the model structure has been discussed, and limitations with the use of the predictive risk equation for progression of AD to FTC[131] have been highlighted. The fact that the model is provided to offer additional information to the NICE Appraisal Committee, to enable them to consider independent analysis on the cost-effectiveness of donepezil, rivastigmine and galantamine in the context of the same modelling methodology and input values for costs and outcomes has also been highlighted.

The model is simplified and does not include consideration of dropouts from treatment (as seen in all trials for these products); this is based on a need to keep the model simple, and it is felt that it is a conservative assumption that favours the intervention. Where dropouts are factored into this modelling approach, additional costs would be expected on the treatment cohort (compared with usual care), with no additional benefits accruing, therefore the estimated cost-effectiveness would be expected to be greater with consideration of dropouts within the disease modelling process. However, it is accepted that it is a limitation of the model.

Good-quality input data for costs or outcomes (health state utilities) have not been identified; however, this appears to be a common problem across all reported cost-effectiveness modelling studies. Furthermore, there is uncertainty over parameter values depicting the proportions of FTC patients by setting (community/institution) and the proportions that are publicly funded when in an institutional setting. Once again these are common limitations in the literature available to inform on modelling disease progression and cost-effectiveness in AD, but these are accepted as limitations in the SHTAC model.

Numerous sources of data have been relied upon to define our cohort of AD patients, and clinical opinion, from a Southampton AD treatment centre, was sought to estimate the additional NHS resources associated with management and monitoring of AD patients on treatment. These are accepted to be limitations with the SHTAC modelling approach.

SHTAC analysis of cost-effectiveness of donepezil, rivastigmine and galantamine using the industry models submitted to NICE

Donepezil – SHTAC adjustments to industry model

The industry model estimating the cost-effectiveness of donepezil uses health states according to disease severity (MMSE categories), and SHTAC have estimated alternative cost inputs for these health states using their cost estimates for pre-FTC and FTC for AD (see above). We use our estimate of pre-FTC for the minimal and mild health states, with moderate AD comprising 50% of patients at pre-FTC, 38.5% at a cost for FTC in the community and 11.5% assumed to be in a health state of FTC in an institution (this later estimate of FTC institution is based on data from Fenn and Gray[91]). For the severe AD health state we assume all patients are in the health state of FTC, with 80% in an institution and 20% receiving FTC in the community. These alternative cost estimates are illustrative of an AD treatment profile, and are provided to consider alternative estimates from the industry model. In addition to the general costs for care of AD, we also add to the drug treatment cohort the cost per year for donepezil 10 mg (£1248) and a monitoring cost (£206, as discussed in SHTAC analysis above). *Table 75* details these alternative cost estimates.

These alterations do not mean that SHTAC have rewired/reworked the model in any way, or that SHTAC accepts the method used in the model. Alternative results are presented here for illustrative purposes only.

Applying the above cost profile to the industry model, keeping all else as presented in the industry model, results in an estimate of £12,975, using deterministic analysis, effectiveness scenario C and half-cycle correction assumptions (industry base case was £7449). Where we also adjust the model to incorporate an increased mortality risk (11% per year), the estimate increases to £13,509. Were these estimates to be based on probabilistic analysis we expect the cost per year in a non-severe AD health state to be well above £15,000 and any subsequent cost per QALY estimate to be in excess of £50,000. This potentially large cost per year of non-severe AD is also based on what we regard as optimistic effectiveness assumptions (using the transit probabilities from one clinical trial), and subsequent alterations to these effectiveness assumptions would also, we believe, have a major impact on the cost-effectiveness results, pushing the cost per year in a non-severe health state to a higher estimate.

Rivastigmine – SHTAC adjustments to industry model

Where SHTAC have used the industry model (deterministic analysis) with alternative inputs to cost data and the utility methods, specified below, we see a cost per QALY of £45,925. These alterations do not mean that SHTAC have rewired/reworked the model in any way, or that SHTAC accepts the method used in the model; alternative results are presented here for illustrative purposes only.

Adjustments made by SHTAC to industry base-case model inputs:

1. Institutionalisation cost set at £18,471 per year, with 70% of this falling on the NHS and PSS budget (£12,929) (base case at £16,380 per year).
2. Home care costs set at £3937 per year (an increase) (base case at £3231).
3. Monitoring cost (additional for rivastigmine treatment) set at £208 per year (a reduction on the base-case cost set at £468 per year).

TABLE 75 *SHTAC cost inputs to donepezil model*

AD severity group	Industry model cost data (£)		SHTAC estimate; components of total care costs (£)			SHTAC total care cost (placebo) (£)	SHTAC total care cost (treatment) (£)
	Placebo	Treatment (including donepezil)	Pre-FTC care	FTC – community care	FTC – institution care		
Minimal	9,515	10,735	100% × 3,973	0% × 5,196	0% × 17,803	3,973	5,427
Mild	13,327	14,548	100% × 3,973	0% × 5,196	0% × 17,803	3,973	5,427
Moderate	17,949	19,170	50% × 3,973	38.5% × 5,196	11.5% × 17,803	6,034.39	7,488
Severe	25,488	25,488	0% × 3,973	20% × 5,196	80% × 17,803	15,282.16	15,282

4. The model estimates of cost-effectiveness are driven by relatively high estimates for utility/QALY gains (compared with published literature and other industry submissions), an incremental gain of 0.0862, but it is difficult to adjust this in a simple SHTAC analysis as it is generated from an equation (predicting a 1-point change in MMSE results in a difference of 0.03 QALY). SHTAC have crudely altered this equation so that the active coefficient of 0.029793 is divided by two, i.e. a 1-point change in MMSE reflects a utility change of 0.015; this results in a prediction of a lower level of utility per change in MMSE, and results in an incremental QALY gain (base case) of 0.0431, essentially halving the benefits seen in the base case industry analysis. This SHTAC alteration is experimental and illustrative only, and has no statistical grounding. However, given that the utility gains in the model are based on differences in MMSE between treatment groups, as shown in *Table 51* **[commercial/academic confidential information removed]**, we note that at 2 years (already 47% dropout in rivastigmine trial) the difference in MMSE is 1.4 points, reflecting a utility difference of 0.041 on the QALY 0–1 scale. (For justification of the cost assumptions for SHTAC parameters, see the text accompanying the SHTAC model on pp. 123–4.)

Galantamine – SHTAC adjustments to industry model

Where SHTAC have used the industry model with alternative assumptions for cost inputs and time frame, it results in a cost per QALY of £49,000, for the galantamine 24-mg dose (all other functions in the model remain the same as in the manufacturer's analysis and no re-wiring of the model has been undertaken). With additional assumptions to reflect a higher mortality rate, we may expect a higher cost per QALY estimate.

Adjustments made by SHTAC to industry base case model inputs:

1. Time frame set at 5 years (base case at **[commercial/academic confidential information removed]**.
2. Cost per month for pre-FTC set to £328 (base case at **[commercial/academic confidential information removed]**).
3. Cost per month for FTC community remains the same at **[commercial/academic confidential information removed]**.
4. Cost per month for FTC institution set at £937 (base case at **[commercial/academic confidential information removed]**).
5. Drug cost increased by £0.60 per day (base case at **[commercial/academic confidential information removed]**) to allow for an additional monitoring cost of £219 per year (i.e. two additional outpatient visits, expected to cost £216 per year). (For justification of these alternative SHTAC parameters see the text accompanying the SHTAC model on pp. 123–4.)

Where only time frame is altered to 5 years from the industry base case of **[commercial/academic confidential information removed]**, all other settings as industry base case, the cost per QALY is £17,385.

Comparison of SHTAC model and analysis with industry cost-effectiveness analysis

Concerns that the methods currently available to model disease progression in AD are suboptimal have been highlighted above, and a critical review of the industry models has been provided. Nevertheless, a model, similar to that used in the industry submission for galantamine, has been developed to consider the cost-effectiveness of donepezil, rivastigmine and galantamine in the treatment of mild to moderately severe AD, comparing these treatments against usual care. The model allows consideration of the three drugs when similar methodology and cost inputs have been used. The results are generally similar across the three drugs (i.e. high cost-effectiveness estimates), with differences by drug treatment driven by the differences in the reported ADAS-cog effectiveness measure used from the clinical review presented in Chapter 4, together with differences in product price.

The cost-effectiveness findings in the current review are markedly different to the published literature and also different to those findings presented to NICE within industry submissions. The published literature is almost entirely comprised of industry-funded studies, and many of the studies are presented from a societal perspective, including patient and caregiver costs outside of the NICE perspective (i.e. NHS and PSS). The literature and the industry submissions are largely driven by optimistic differences in effectiveness of treatment, compared with usual care, using either unpublished transition probabilities from clinical trials or effectiveness findings that are uncertain in the context of the

general clinical trial literature (e.g. effect of treatment on psychotic symptoms).

As the drug treatments are portrayed as having benefits in terms of delaying disease progression (to severe AD or to FTC), the cost structure in the CEA is very important, and central in driving the findings, that is, if severe AD (or FTC) is described as being very resource intensive and expensive, then the drug treatment will be seen as more attractive if it is assumed it will offer cost savings by reducing the time a patient spends in such a disease/health state. Most if not all studies raise some concerns over the way they structure the cost of care for AD. Our estimates presented above relate to costs of care for AD in the context of health states describing pre-FTC and FTC (in SHTAC analysis), and find that many studies use costs in excess of those suggested in our review. It has been highlighted that not all long-term institutional costs will fall on the NHS and PSS budget, and many patients with AD will either be self-funding in institutional care or part-funded, and some allowance for this made in the cost estimates used. None of the cost studies or cost-effectiveness studies identified have discussed this issue or made allowance in analysis. From our sensitivity analysis this issue has a big impact on cost-effectiveness findings.

Some alternative cost assumptions in the industry models for donepezil, rivastigmine, and galantamine are highlighted and the resultant cost-effectiveness estimates from the models presented. Where only cost input alterations to the donepezil model have been made it suggests findings indicative of a cost-per QALY of £50,000 (deterministic analysis, and we suggest probabilistic analysis will give a higher cost per QALY). It is felt by the present authors that this adds some support to the findings in the SHTAC model, given that the industry submission makes a number of other optimistic inputs related to treatment effectiveness.

For rivastigmine it was not felt that the cost structure of the industry model is far from our view, although estimates related to monitoring are some way apart (industry cost for monitoring does not favour rivastigmine, as it is much higher than the SHTAC estimate). Where amendments are made to the assumption on utility weightings in the model a resultant cost per QALY in the region of £50,000 (using deterministic analysis) is seen, and the findings offer some support for the estimates presented by SHTAC against the cost-effectiveness of rivastigmine, given the use in the rivastigmine model of effectiveness data from a longer term open-label study that shows findings potentially subject to serious bias.

Where SHTAC have made adjustments to the industry model for galantamine the cost per QALY findings (over 5 years) are not drastically different from those in the SHTAC model, with the observed difference potentially attributable to the differences in the modelling of mortality, the use of an additional monitoring cost and the use of an additional effectiveness impact in the industry analyses (i.e. difference in presence of psychotic symptoms). Furthermore, there are structural differences in the SHTAC model compared to the industry model.

Overall, it is noted that given the relatively small incremental health gains, e.g. QALY gains, presented in the cost-effectiveness analysis for these treatments, the subsequent cost-effectiveness summary statistics (e.g. cost per QALY) are very sensitive to relatively small changes to the estimated incremental costs; e.g. where incremental QALY gains are 0.04, it takes an incremental cost of only £2000 (which may not be regarded as substantive or prohibitive in some cases over a 5-year period) to produce a cost per QALY of £50,000.

Summary: cost-effectiveness analysis for mild to moderately severe AD

The clinical effectiveness review (Chapter 4) reported findings from RCTs, indicating that drug treatments (donepezil, rivastigmine and galantamine) show statistically significant benefits across various outcome measures (e.g. cognitive outcomes, global health outcomes) in the treatment of mild to moderately severely AD. However, the link from clinical trial outcomes to longer term patient-related outcomes (e.g. delay in disease progression, reduction in institutionalisation) is largely absent in the current literature, with modelling studies used to predict disease progression over time. The difficulties present in estimating cost-effectiveness for these treatments in AD is discussed above, in some detail; however, accepting these difficulties, the findings from the cost-effectiveness review and analysis for donepezil, rivastigmine and galantamine in mild to moderately severe AD are summarised below.

Generally, published cost-effectiveness studies and the industry submission are varied in their methods, and offer an unclear picture owing to differences in methodological approaches,

perspective employed and the effectiveness data used to model disease progression. Almost all studies are sponsored by industry. Cost savings are predicted in a number of studies, although many of these are from a societal perspective and include caregiver time costs and expenses. Cost calculations are largely driven by the high costs associated with FTC of AD patients, particularly when institutionalised, and the assumption that treatment may delay disease progression and the costs associated with FTC.

Cost-effectiveness of donepezil

Nine published economic evaluations of donepezil and the industry submission have been reviewed and two abstracts have been summarised. All studies other than those from Stein[81] and the AD2000 trial[43] are regarded as industry sponsored (either fully or in part). As can be seen from the 'headline findings/predictions' reported in *Table 48*, the studies produced a variety of conclusions regarding the cost-effectiveness of donepezil with studies reporting that treatment was cost saving,[83–85,87,89] cost neutral,[82] cost incurring[43,86,88] or cost incurring for the health care system but cost saving for patients and caregivers.[56] This wide range of conclusions is perhaps not surprising given the diverse country settings, variations in the perspective of the studies and differences in the types of resources that were included in the cost estimates and also the differences in the way in which the models used were constructed.

All the studies seem to agree that costs are higher in severe AD and that most of this increased cost is that associated with institutional care (e.g. nursing/residential home). Therefore, it is assumed that a cost saving can be achieved by delaying progression to the more severe AD state. However, a key assumption in the models is that cost of care is related to level of cognitive ability, and persons with a low (more severe) MMSE score incur greater costs of care. This, however, may not be an accurate assumption, as the ability to perform everyday tasks (functional ability as measured by activities of daily living indices) may also be a significant determinant of whether or not a person needs institutional care.[122]

There are concerns over the use of MMSE in the cost-effectiveness studies, as it has limitations for defining disease severity, and also in the modelling of disease progression in AD. One of the greatest difficulties is the test–retest and inter-rater variation that occurs, which can give rise to fluctuations in recorded scores that do not reflect changes in cognition but which may actually mask any small true change. This is a particular problem in short-term clinical trials when the changes in cognition may be small over the trial period. There are also concerns around the methods and data used to consider mortality in what is a very elderly patient group.

Cost-effectiveness studies report varied results. Whereas a number of studies predict cost savings over time (often based on the inclusion of informal care and patient costs[85] or healthcare systems dissimilar to the UK[87]), studies by Stein,[81] Stewart and colleagues,[82] Neumann and colleagues,[86] the AD2000 trial[43] and others,[56,88,89] predict additional incremental costs associated with treatment, alongside benefits associated with changes in cognitive function. Some interpretation is required on whether these benefits are classed as meaningful in the context of the additional costs.

The simple study by Stein[81] suggests that donepezil is not cost-effective. Where Stewart and colleagues[82] discuss a cost of between £1200 and £7000 per year in a non-severe state, it is important to consider that it is the difference in QoL between severe and non-severe, for example in the context of a QALY, that is pertinent for cost-effectiveness, that is, how does the patient/society value the endpoint. The industry submission suggests a base-case cost per year in a non-severe state of £1206, with results presented with half-cycle correction and using probabilistic analysis suggesting the cost per year of non-severe AD to be £10,826. However, given the issues discussed above, it would appear reasonable in the context of the sensitivity analysis presented to conceive of a cost per QALY well in excess of £40,000–50,000 (based on potentially optimistic effectiveness data).

Cost-effectiveness analysis by SHTAC, using the cost-effectiveness model described above, suggests that donepezil treatment has a cost per QALY in excess of £80,000. Incremental QALY gains are small over 5 years and additional costs to the NHS and PSS, largely comprising the cost for donepezil treatment, are in the region of £3000. The model suggests that donepezil treatment reduces the time spent in FTC (delays progression to FTC) by 1.42–1.59 months, but cost savings associated with this reduction do not offset the cost of treatment sufficiently to make it appear a cost-effective intervention.

Cost-effectiveness of rivastigmine

The above review has discussed four published economic evaluations reporting on the cost-

effectiveness of rivastigmine,[90–93] together with the industry submission and one published abstract.[94] Cost-effectiveness studies for rivastigmine and the industry submission are based almost solely on methods involving MMSE as a measure of cognitive function, with rivastigmine treatment related to delays in cognitive function and patient benefits over time. The methodology used is based on an assumption that these delays in cognitive decline (as measured by MMSE) translate into meaningful patient outcomes, and this review has highlighted uncertainties over the validity of using the MMSE alone to model disease progression. The two UK studies[90,91] and the industry submission report additional costs associated with rivastigmine treatment (the relatively small cost savings reported by Fenn and Gray[91] would be offset once drug costs were included in the analysis). The studies by Hauber and colleagues[92,93] are for the USA and Canada and do not report sufficient detail for us to be confident on the cost calculations applied, the USA study does not include drug costs and the Canadian Study is from a societal perspective including costs for informal caregiver time. The industry submission reports a baseline cost per QALY of £24,600; however, concerns over the methods used have been highlighted and it may be that this is an underestimate of the cost-effectiveness of rivastigmine treatment. Where assumptions are made above related to cost inputs, the cost per QALY remains below £29,000, but with subsequent alteration to the inputs for health state utility (QALYs) the cost per QALY rises to £45,925.

Cost-effectiveness analysis by SHTAC, using the cost-effectiveness model described above, suggests that rivastigmine treatment has a cost per QALY in excess of £57,000. Incremental QALY gains are small over 5 years and additional costs to the NHS and PSS, largely comprising the cost for rivastigmine treatment, are in the region of £2100–2300. The model suggests that rivastigmine treatment reduces the time spent in FTC (delays progression to FTC) by 1.43–1.63 months, but cost savings associated with this reduction do not offset the cost of treatment sufficiently to make it appear a cost-effective intervention.

Cost-effectiveness of galantamine

Cost-effectiveness studies for galantamine are very similar in methods, and reflect country-specific analyses; all are sponsored by the manufacturer. Clinical trials have shown statistically significant differences in outcomes between galantamine and placebo, but these outcomes need some interpretation in the context of patient experiences over the longer term, in terms of disease progression and the need for FTC and institutionalisation. The cost-effectiveness literature has attempted to extrapolate to long-term patient outcomes, using the need for FTC. Published studies show various country-specific analyses, consistently reporting that treatment with galantamine results in a delay to requiring FTC (approximately 2.5–3 months over a 10-year time horizon), but the generalisability of cost-effectiveness studies to the UK is limited owing to country-specific analyses (e.g. Getsios and colleagues[95] use unit costs for hospitalisation that are excessive compared with UK costs, and Garfield and colleagues[96] include paid caregiver time). The UK study by Ward and colleagues[99] reports a cost per QALY of £8693 for 16-mg galantamine treatment and £10,051 for 24-mg galantamine (the industry submission uses cost-effectiveness estimates from Ward and colleagues), but concerns over the methods employed have been highlighted above, and suggest that this is an underestimate of the cost-effectiveness of treatment. SHTAC present results from the industry model using alternative parameter and time-frame inputs, and report a cost per QALY of over £49,000.

CEA by SHTAC, using the cost-effectiveness model described above, suggests that galantamine treatment has a cost per QALY in excess of £68,000 per QALY. Incremental QALY gains are small over 5 years and additional costs to the NHS and PSS, largely comprising the cost for galantamine treatment, are in the region of £2650–2850. The model suggests that galantamine treatment reduces the time spent in FTC (delays progression to FTC) by 1.54–1.73 months, but cost savings associated with this reduction do not offset the cost of treatment sufficiently to make it appear a cost-effective intervention.

SHTAC cost-effectiveness analysis for memantine for moderately severe to severe AD

Published studies and the industry submission use the same modelling methods when estimating the cost-effectiveness of memantine, modelling disease progression over time using transition probabilities for health states described using severity, dependency and location.

This model has not been replicated; an outline description and review of the model is provided,

indicating that although intuitively attractive the model contains data that cast serious doubt on the validity of the results presented. Illustrative findings are presented below from the use of the industry model with some alternative parameter inputs (below) to determine alternative estimates of cost-effectiveness for memantine versus usual care (no drug therapy). It is suggested that similar issues are relevant to the consideration of the cost-effectiveness of memantine where it is compared with usual care including donepezil treatment.

Memantine – SHTAC adjustments to industry model

Where SHTAC have used the industry model with alternative assumptions, for cost inputs, QALY values and discount rates, as in *Table 76*, the model estimates a cost per QALY between £37,000 and £53,000 (depending on assumption on percentage of institutional costs met by the NHS and PSS) for memantine versus no pharmacological therapy (all other functions in the model remain the same as in the manufacturer's analysis; no re-wiring of the model has been undertaken). Where we have commented above on the optimistic or uncertain nature of transit probabilities used, and the weak evidence underlying these data, we have not been able to use alternative assumptions in the model, therefore the above SHTAC estimate is also based on these data, and any further adjustments to model effectiveness data (to offer a more

TABLE 76 *SHTAC adjustments to the industry model for cost-effectiveness of memantine*

	Industry (per 6-month cycle)	SHTAC alternative (per 6-month cycle)	Rationale for SHTAC adjustment
Costs			
Community dependent	£5,670	£2,589	SHTAC cost estimate for full-time-care (FTC) in the community (see *Table 71*)
Community independent	£2,234	£1,969	SHTAC cost estimate for pre-FTC costs [see the section 'SHTAC cost-effectiveness for mild to moderately severe AD' (p. 133)]
Institution dependent	£32,919	£11,672	Industry estimates high and evidence base uncertain
Institution independent	£21,102	£10,220 (£8,901 and £7,450 respectively, where 70% of patients are publicly funded)	We see institutional costs as the main cost driver for institutionalised patients regardless of level of dependency. Therefore, we see little difference between the cost for institutionalised patients by dependency. For both dependency levels we use an annual cost for institutional care of £18,471 from Netten *et al.*[130] For dependent patients we add to this the estimate of additional NHS resource use for severe AD patients, £4874 per year, from Kavanagh and Knapp[185] and Ward *et al.*[99] (see *Table 71*, and related text). For independent patients we use annual institutional costs, plus 50% of the estimated cost for community independent AD patients (£1969 per year/£985 per cycle). We recognise that these cost estimates are crude, but see them as more realistic than the industry cost estimates
QALYs			
Independent	0.65	0.455	The industry utility estimates are from a sample that comprises predominantly mild and independent AD patients, whereas the model is based on moderately severe to severe patients. We use data from Neumann *et al.*,[187] who report values for moderate AD and severe AD by community and institutional setting (see *Table 66*). We use an average (across moderate and severe AD) of community values as an estimate for 'independent', and an average of institutional values as an estimate for 'dependent', for use in the memantine patient group
Dependent	0.32	0.395	
Discount rates			
Costs	3.5%	6%	NICE guidance for current wave of appraisals
Outcomes	3.5%	1.5%	

conservative effectiveness scenario) would result in a higher cost per QALY estimate.

Summary: cost-effectiveness analysis for memantine, moderately severe to severe AD

The clinical-effectiveness review (Chapter 4) reported findings from RCTs, reporting that memantine has shown statistically significant results in clinical trials (functional, global and cognitive outcomes). However, as with the discussion of treatments above for mild to moderately severe AD, the link between trial outcomes and longer term patient-related outcomes (e.g. delay in disease progression, institutionalisation) are not clear. The findings from the cost-effectiveness review and analysis for memantine in moderately severe to severe AD are summarised below.

Cost-effectiveness of memantine

It is difficult to draw conclusions on the cost-effectiveness of memantine. The clinical effectiveness of memantine is reported in Chapter 4 and the RCTs report differences in memantine compared with usual care across various dimensions of AD, the interpretation of which in the context of meaningful patient outcomes is required to consider cost-effectiveness. A resource utilisation study by Wimo and colleagues[147] reporting on costs associated with patient groups in the 6-month RCT by Reisberg and colleagues[72] (placebo versus memantine) indicates cost differences from a societal perspective, but where a third-party payer perspective is taken (e.g. NHS and PSS), cost difference appears negligible, excluding the drug cost for memantine.

Five economic evaluations reporting on the cost-effectiveness of memantine were identified.[100–104] Cost-effectiveness studies report cost reductions and improved outcomes; however, these are based on a number of assumptions. Those studies reporting non-UK cost-effectiveness estimates are based on a societal perspective and are not helpful in the UK context. Cost-effectiveness studies and the industry submission use similar modelling methods to estimate cost-effectiveness. The UK study by Jones and colleagues[104] and the industry submission contain data (on transit probabilities, costs, QALYs) that raise serious doubts over the validity of the results reported, in the context of the UK treatment population. Where SHTAC have made adjustments to the cost inputs and health state utility inputs, the estimated cost per QALY (all other model functions and inputs remaining constant, with drug cost at 2004 price) is in the range £37,000–52,000 (memantine versus usual care with no drug therapy). Further amendments to the potentially optimistic transit probabilities (measure of effect) would, in our opinion, offer higher cost per QALY estimates.

Chapter 7

Research in progress

Ongoing research, with relevance to the assessment of donepezil, rivastigmine, galantamine or memantine for AD, is described below.

The EXCEED study is a prospective, 24-month, multicentre, multinational, randomised, double-blind, parallel group study comparing treatment with rivastigmine with treatment with donepezil. Participants in the trial are classed as moderate to moderately severe AD (MMSE score of 10–20) aged 50–85 years. Outcome measures include the SIB, the GDS, ADCS/ADL, NPI, NPI-D and MMSE and use of concomitant psychotropic medications. The EXCEED study is funded by Novartis (manufacturers of rivastigmine) and at the time of writing is expected to complete in late 2004.

A pilot study comparing the effect of galantamine with donepezil in patients with moderate or severe AD is currently ongoing. This is a multicentre, randomised, rater-blinded study. Outcomes include the effect on behavioural symptoms, cognition, ADLs and resource utilisation. This study is funded by Shire (manufacturers of galantamine). The expected completion date was not available.

The 'Memantine once daily dosing and simplified dose titration study' is a multicentre, double-blind randomised controlled trial of patients with moderately severe to severe AD. Outcomes include safety, vital signs and the CGIC scale. This study is funded by Lundbeck (manufacturers of memantine) and at the time of writing is expected to complete in late 2004.

Chapter 8

Implications for other parties

If drug therapy stabilised some of the symptoms of AD for even a limited period of time, the QoL of patients and carers may be affected. Carers of people with AD are often family members and are often elderly themselves. Any improvement in symptoms that leads to greater independence of the person with AD may reduce some of the physical and emotional responsibilities for the carer. If drug therapy was effective in delaying institutionalisation, this would have an impact on patients, their carers and other parties. In particular, there would be continued need for further support from the wide range of agencies which currently supply services for patients and their carers in the community.

The sparse literature on the costs associated with AD reports that a significant proportion of the cost of caring for AD falls on patients and caregivers. A review of nine studies on costs for community-based people with AD estimated that the proportion of total costs represented by informal care ranges between 36 and 85%.[188] This wide range is in part due to differences in the type of costs included and the methods used to quantify and value caregiver time. O'Shea and O'Reilly,[152] in a cost study of AD in Ireland, report that family care accounts for almost 50% of the overall resource burden for AD (based on an opportunity cost valuation of carer time). It is difficult to estimate the impact on informal costs, and/or caregiver time, from treatment with the pharmaceuticals discussed in this review, owing to the varied methodology and coverage of these issues in published cost and cost-effectiveness studies, but consideration should be given to the significant inputs of time and resource by care-givers to the treatment of AD and to the costs met by AD patients themselves in the management of this disease.

Chapter 9

Factors relevant to NHS policy

The increasing numbers of the very elderly will increase demands on services. If the drugs are effective in delaying institutionalisation, there may be more demand on currently available community services, where there are currently resource issues around the numbers of available professional carers. On the other hand, this may reduce some of the cost and capacity issues around service provision in institutions (care homes, nursing homes). The cost of treatments with these drugs for a proportion of AD patients needs to be considered along with the other competing uses of funds for AD such as support for carers (e.g. respite care, night-sitters).

Previous NICE guidance[30] projected an expected annual drug cost for donepezil, rivastigmine and galantamine (combined) at £42 million, commenting that this may have been an overestimate as it did not account for those patients dropping off therapy, although the projection was for a 'steady state', allowing for incidence of AD and for patients having an average treatment period of 36 months. The Department of Health prescription cost analysis (PCA)[189] for 2003 reports prescription costs for these drugs (community prescriptions) at a total of £31 million (net ingredient costs), excluding a cost of £636,000 on the prescribing of memantine. Donepezil prescribing comprised £23.5 million (76%) of this expenditure. Prescribing of these products in AD, as reported for 2003, may not have reached the 'steady-state' predictions of the NICE guidance, but prescribing practice would have had 2–3 years to develop. Furthermore, the prescribing data from the PCA is not limited to AD, and it would be expected that some prescribing would have been in the non-AD dementia patient groups, although this may form a very small proportion of prescribing expenditure at the present time. Some additional prescribing costs from non-community-dispensed prescriptions would also be expected.

Given that memantine has been introduced for patients with moderately severe to severe AD, it presents as an additional prescribing cost to the NHS, at a price of £900 per year (from March 2005) for the 20-mg daily dosage (as used in the two included RCTs). Following from earlier NICE guidance and predicting that around 15,000 patients per year may be treated with memantine, there could be an additional prescribing cost in the region of £14 million per year, where memantine was prescribed for moderately severe to severe AD, although it might take a number of years before prescription of this product reached such a large patient group. Where the potential patient group was predicted to be smaller, with a limited uptake from physicians, at around 5000 patients per year, additional prescribing costs would be in the region of £5 million per year.

The industry submission (Lundbeck) to NICE for memantine predicts a potential treatment group of 23,448 moderately severe to severe AD patients, with a mean treatment period of around 6 months, calculating a prescribing cost for memantine at approximately £10.9 million per year (with this level of prescribing not being reached until year 2, following a positive recommendation/guidance from NICE).

In addition to the prescription cost for products discussed, there will also be an additional cost burden on the NHS related to additional monitoring of patients while on treatment. It is suggested that this resource use may be limited to two additional outpatient appointments per year while on treatment, approximately £216 per year per patient treated. Any potential cost savings, due to possible delays in institutionalisation, are likely to be felt by the PSS sector rather than the NHS.

Chapter 10

Discussion and conclusions

Statement of principal findings

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

Efficacy in interventions for mild to moderately severe AD

Donepezil

Thirteen published RCTs and one unpublished RCT of mixed methodological quality were included in the review. There is evidence from studies using cognitive and global outcome measurement scales that donepezil appears to be beneficial in AD. The benefit varies according to the dose, with higher doses of donepezil tending to show increasing benefit. These higher doses relate to the therapeutic dose used most often in clinical practice. The benefit on cognition and global outcome is also maintained over study durations of approximately 1 year. Donepezil appears to have some effect in improving or limiting further deterioration on ADLs over periods ranging from 12 to 24 weeks, but over 1 year this effect is limited. The number of different measures of ADL used in the included studies, however, make overall conclusions difficult to draw. There is also less conclusive evidence of effectiveness on behaviour and mood; again in the shorter term (12–24 weeks) donepezil may be beneficial. Few included studies measured behaviour and mood. The effects of donepezil on QoL are mixed, but no studies used scales that had been validated in these populations. Adverse events are more common with higher doses of donepezil, although they are associated with treatment with donepezil generally. The majority of adverse events are gastrointestinal in nature. A number of issues and methodological concerns which may have some bearing on the interpretation of this evidence are discussed below.

Rivastigmine

Four published RCTs and two unpublished RCTs met the inclusion criteria for the review. The quality of reporting was varied and no trial lasted longer than 26 weeks. A range of doses of rivastigmine were investigated across the studies; some used fixed dosing regimens and others were flexible dose studies. These factors make the interpretation of the evidence more difficult. There is evidence from studies using cognitive and global outcome measurement scales that rivastigmine may be beneficial in AD and that this is particularly so at higher doses (6–12 mg). On cognitive measures benefit was demonstrated in two of three studies for the higher doses of rivastigmine only. On global measures benefit was similarly demonstrated with the higher doses of rivastigmine only. Rivastigmine also appears to be beneficial at higher doses on measures of function, although this was not always demonstrated with statistical significance. On measures of behaviour and mood (two studies only) there was no reported beneficial effect of rivastigmine compared with placebo. Adverse events were more common with higher doses of rivastigmine, although nausea and vomiting were associated with treatment generally. A number of issues and methodological concerns which may have some bearing on the interpretation of this evidence are discussed below.

Galantamine

Six published RCTs and one unpublished RCT of variable methodological quality were included in the review. No studies had a duration of follow-up longer than 6 months. There is evidence from studies using cognitive and functional outcome measurement scales that galantamine may be beneficial in AD. The benefit on cognitive outcomes varies depending on the dose of galantamine, with higher doses tending to relate to improved cognition. Improvements on measures of function were also demonstrated with galantamine at higher doses. On global outcome measures, individual studies show higher proportions of participants improving with galantamine, but this is not reflected in the meta-analysis. Galantamine had some effect in improving or limiting further deterioration on measures of behaviour and mood, although this was only statistically significant in one of three of the included studies that reported this as an outcome. Galantamine has associated adverse events, mainly gastrointestinal in nature. In some trials considerably more participants withdrew owing to adverse events, this following a

dose–response relationship. A number of issues and methodological concerns which may have some bearing on the interpretation of this evidence are discussed below.

The results of the present review show the same trends as noted in previously published systematic reviews.

Direct comparisons between cholinesterase inhibitors

When directly compared with donepezil in two trials, treatment with rivastigmine showed no statistically significant differences on measures of cognition or function.

In a study directly comparing donepezil with galantamine, both treatments showed improvement on measures of cognition and function. The improvement with donepezil was shown to be greater however, and adverse events were shown to be more common in the galantamine patients.

Efficacy in interventions for moderately severe to severe AD

Memantine

Two RCTs of good methodological quality were included in the review. In these studies different participant groups were used; in one study participants were already receiving donepezil. Both studies were of a relatively short duration of approximately 6 months. Memantine shows beneficial effects in participants with moderately severe to severe AD in terms of functional and global measurements, where participants in the treatment arms show less deterioration than those in the placebo arm. The effect of memantine on cognitive outcome measurements is also favourable, although this was not always statistically significant. On measures of behaviour and mood, memantine was only beneficial in the groups already receiving donepezil. There was a tendency for more adverse events with treatment with memantine, but withdrawals due to adverse events tended to be greater in the placebo groups. Overall, the results suggest that memantine may be more effective in patients who are already receiving and continue to receive donepezil, but this is tentatively based on one trial only. A number of issues and methodological concerns which may have some bearing on the interpretation of this evidence are discussed below.

The results of the present review show the same trends as noted in previously published systematic reviews.

Cost-effectiveness

Cost-effectiveness for treatment of mild to moderately severe AD

Cost-effectiveness of donepezil

Nine published economic evaluations of donepezil and the industry submission have been reviewed, together with a summary of two published abstracts. Except for those by Stein and the AD2000 collaborative group, these studies are regarded as industry sponsored (either fully or in part). Studies have presented a variety of conclusions regarding the cost-effectiveness of donepezil, with donepezil as cost saving, cost neutral or cost incurring; however all studies present donepezil as having a beneficial effect on cognitive function. The wide range of results seen in the literature is perhaps not surprising given the diverse country settings, variations in the perspective of the studies and differences in the types of resources that were included in the cost estimates, and also the differences in the way in which the models used were constructed.

The international literature is not helpful in the context of a UK analysis, given the societal perspective often employed, and the cost structures used for cost-effectiveness analysis in a non-UK setting. Where UK-specific analysis is seen, the simple study by Stein suggests that donepezil is not cost-effective and Stewart and colleagues discuss an incremental cost of between £1200 and £7000 per year in a non-severe AD health state. When considering the findings from Stewart and colleagues, it is important to note that it is the difference in QoL between severe and non-severe, for example in the context of a QALY, that is pertinent for cost-effectiveness, that is, how does the patient/society value the endpoint. The industry submission suggests a base-case cost per year in a non-severe state of £1206, with results presented with half-cycle correction and using probabilistic analysis suggesting the cost per year of non-severe AD to be £10,826. However, given the issues discussed above, it would appear reasonable in the context of the sensitivity analysis presented to conceive of a cost per QALY well in excess of £40,000–50,000 (with this estimate also based on potentially optimistic effectiveness data).

Cost-effectiveness analysis by SHTAC, using the cost-effectiveness model described above, suggests that donepezil treatment has a cost per QALY in excess of £80,000 per QALY.

Cost-effectiveness of rivastigmine

Four published economic evaluations reporting on

the cost-effectiveness of rivastigmine have been reviewed, together with the industry submission and and one published abstract. Cost-effectiveness studies for rivastigmine and the industry submission are based almost solely on methods involving MMSE as a measure of cognitive function, with rivastigmine treatment related to delays in cognitive function and patient benefits over time. The two UK studies and the industry submission report additional costs associated with rivastigmine treatment (the relatively small cost savings reported by Fenn and Gray would be offset once drug costs were included in the analysis). Studies by Hauber and colleagues are for US and Canadian analysis and do not report sufficient detail for us to be confident on the cost calculations applied; the USA study does not include drug costs and the Canadian Study is from a societal perspective including costs for informal caregiver time. The industry submission reports a baseline cost per QALY of £24,600, but there are concerns highlighted over the methods used, and it may be that this is an underestimate of the cost-effectiveness of rivastigmine treatment. Where assumptions are made related to cost inputs, the cost per QALY remains below £29,000, but with subsequent alteration to the inputs for health state utility (QALYs) the cost per QALY rises to £45,925.

Cost-effectiveness analysis by SHTAC, using the cost-effectiveness model described above, suggests that rivastigmine treatment has a cost per QALY in excess of £58,000.

Cost-effectiveness of galantamine

Five cost-effectiveness studies for galantamine have been reviewed, all with very similar methodology, presented to report country-specific analyses (one UK study), and all studies were sponsored by the manufacturer. Clinical trials have shown statistically significant differences in outcomes between galantamine and placebo, but these outcomes need some interpretation in the context of patient experiences over the longer term, in terms of disease progression and the need for FTC and institutionalisation. The cost-effectiveness literature has attempted to extrapolate to long-term patient outcomes, using the need for FTC. Generalisability of findings from non-UK studies is limited owing to country-specific costing in analyses and the inclusion of caregiver cost in some studies. The UK study by Ward and colleagues reports a cost per QALY of £8693 for 16-mg galantamine treatment and £10,051 for 24-mg galantamine (the industry submission uses cost-effectiveness estimates from Ward and colleagues), but concerns have been highlighted in this report over the methods employed, and the findings from Ward and colleagues and the industry submission are thought to underestimate the cost-effectiveness (cost per QALY) of treatment. SHTAC present results from the industry model using alternative parameter and time-frame inputs, and report a cost per QALY of over £49,000.

Cost-effectiveness analysis by SHTAC, using the cost-effectiveness model described above, suggests that galantamine treatment has a cost per QALY in excess of £68,000.

Cost-effectiveness for treatment of moderately severe to severe AD

Cost-effectiveness of memantine

It is difficult to draw conclusions on the cost-effectiveness of memantine. Five economic evaluations reporting on the cost-effectiveness of memantine have been considered (three abstracts and two in press studies). Cost-effectiveness studies report cost reductions and improved outcomes; however, these are based on a number of assumptions. Those studies reporting non-UK cost-effectiveness estimates are based on a societal perspective and are not helpful in the UK context. Cost-effectiveness studies and the industry submission use similar modelling methods to estimate cost-effectiveness. The UK study by Jones and colleagues and the industry submission contain data (on transit probabilities, costs, QALYs) that raise serious doubts over the validity of the results reported, in the context of the UK treatment population. Where SHTAC have made adjustments to the cost inputs and health state utility inputs, the estimated cost per QALY (all other model functions and inputs remaining constant) is in the range £37,000–52,000 (memantine versus usual care with no drug therapy). It is suggested that further amendments to the potentially optimistic transit probabilities (measure of effect) would offer higher cost per QALY estimates.

Other issues and methodological concerns

A number of issues that need to be taken into account when considering the results of the present review are noted below.

Quality of reporting

The quality of reporting of important design issues was only moderate among included clinical effectiveness studies. The method of randomisation was not always described. In addition, most studies made no mention of any

efforts to conceal the allocation of patients to treatment groups. This is a major shortcoming that potentially can lead to selection bias. Most studies were reported to be double-blind, but blinding of the outcome assessors was demonstrated in only a few. Studies tended to report results as LOCF, with limited reporting of results using ITT analysis. These factors may have an effect of overestimating the treatment effect.

Length of follow-up

It is important to demonstrate whether these interventions can have lasting effects. Ideally, trials would report on interventions given over, and evaluated after, a reasonably long duration, for example 12 months or more. However, there were few RCTs and no CCTs with a long period of follow-up. Of those RCTs that did follow patients over longer periods there were often high dropout rates. The likelihood of further longer term trials is reduced, however, owing to a lack of clinical equipoise.

Attrition

Many included studies had fairly high levels of dropout between initial recruitment and reporting of results. In many studies a large proportion of those dropping out were due to adverse events. High attrition rates affect the validity of study results, but they are also a practical concern. If an intervention results in very high attrition rates within a trial, then this may be reflected in clinical care. Dropouts after randomisation can be compensated for in an ITT analysis; however, very few studies here undertook an adequate ITT analysis. LOCF analysis may produce a bias, especially when there is non-random dropout between study groups.

Dose comparisons

A number of trials report more than one dose of the intervention drug, generally showing that higher doses provide more benefit. However, this can only be inferred from the data provided, as statistical comparisons between doses have not been made in most cases.

Meta-analysis

In many cases individual trials were omitted from the meta-analysis for one or more of a number of reasons. In many publications the data presented were in a graphical form only. Although data were estimated it was often not possible to extract or calculate the measures of variance around the point estimates and therefore these trials could not be included in the meta-analysis. Many trials report different dosages of the treatment drug and only where similar doses were reported was it possible to combine data. Some trials had populations that the reviewers felt were too dissimilar for pooling, for example, moderately severe patients only or those who had already undergone treatment with the treatment drug prior to randomisation. In all cases only data reported to be from the ITT population were pooled.

Outcome measures

A number of measurement scales for assessing global change, cognition, functional ability and behaviour and mood were used in the included trials. It is difficult to know what the changes demonstrated on each measure really mean; improvements in many cases were small, and may not be clinically significant. The European Agency for the Evaluation of Medicinal Products[190] suggest a 'responder' for mild to moderately severe dementia as a person who meets three criteria: improved cognitive function (usually ≥ 4 points on ADAS-cog); improvement or stabilisation on a global clinical impression scale completed by caregivers (e.g. CGIC or CIBIC-plus); improvement of stabilisation on daily activities (e.g. IADL, PDS). For moderately severe to severe dementia they suggest using the last two criteria only as cognitive improvement is unrealistic.

Very few studies presented data that would relate to all of these criteria. Five studies falling into the category of treatments for mild to moderately severe AD report the proportion of participants gaining at least 4 points on the ADAS-cog. Despite all showing a greater proportion of participants in the treatment groups than the placebo groups, these differences were not always statistically significant. On CIBIC-plus scales a number of studies demonstrated higher proportions of participants in the treatment groups 'responding' with a score of <3. Of those studies reporting functional outcomes, in many cases there was a difference between the groups shown, but often this was a demonstration of less deterioration on ADLs in the treatment group compared with the placebo group.

The majority of the scales used have been shown to be reliable and valid tools; however, there is evidence of variability in most of the outcomes reported in the included trials. The range of scores is often large; some patients will have improved, others will have stayed the same, while others will have deteriorated. This variance should be comparative in both the treatment and the

placebo groups but care should be taken over the interpretation of the mean scores.

The use of mean scores is necessary for the purposes of a trial; however, it is not known what the effects of the drugs are on an individual.

The outcome measures used are proxy measures that may not reflect outcomes that are important to people with AD or their carers. Results from the AD2000 trial,[43] for example, suggest that measures of cognition do not necessarily correlate with important outcomes such as activities of daily living. In addition, the limited use of QoL measures, whether directed at the person with AD or their carers, also makes interpretation of what the results really mean more complicated.

Participant characteristics

Patients included in the studies had been diagnosed using recognised criteria. The criteria used to distinguish the severity of disease differed between included trials. For those thought to have mild to moderately severe AD, the MMSE was used in most cases, with the range falling between 10 and 26. Two studies were included that described their population as mild to moderate without using the MMSE. A pragmatic decision was taken in the present review to use the definition reported in individual trials, therefore ensuring that all studies with a population described as mild to moderately severe AD would be included. This was in part due to the growing concern that while the MMSE is a reasonable screening tool, it has a large degree of variability.[178,191] For those thought to have moderately severe to severe AD the review did not stipulate how this should be defined; however, the MMSE was used in both included trials, with ranges falling between 3 and 14.

Patients with coexisting illness or concurrent treatment were often excluded from the included trials, providing a healthier patient population than might be seen in practice. In the AD2000 trial,[43] the population was reported to be more representative of clinical practice, although patients were those for whom the recruiting clinician was uncertain about the potential benefit of the medication. In this trial the evidence of clinically relevant benefit was less clear.

In some cases studies have commented on lack of improvements in some outcomes where there may have been little room for improvement. For example, on behavioural measures, some studies report no improvements in behaviour but the majority of patients entering these studies had no behavioural problems.

One trial[192] that did not meet the inclusion criteria as it did not state that the population was mild to moderately severe AD and the MMSE was 9–18, which fell just outside of the 10–26 range, did undertake a subgroup analysis on those with an MMSE of 12–18. Although this study was technically an exclusion from the review, because of the difficulties with defining disease severity noted above, the subgroup analysis has been summarised here. The study compared galantamine with donepezil over 52 weeks. Although galantamine patients demonstrated a worsening in the ADAS-cog score compared with baseline, this worsening was less than in the donepezil group (1.61 ± 0.80 galantamine, versus 4.08 ± 0.84 donepezil, $p < 0.05$). On the MMSE a similar pattern was shown. No statistically significant difference in change from baseline score was shown on the Bristol ADL scale. These results are different from those of the one included trial that compared donepezil with galantamine where donepezil was shown to have larger effects, and therefore the results of this comparison may need to be interpreted more cautiously.

Cost-effectiveness analysis

There is a limited literature on the costs associated with AD and on the patient-related outcomes or endpoints of interest (e.g. rate of delay in disease progression, dependency levels and need for increasing level of caregiver support and rate of institutionalisation). A great deal of the cost-effectiveness literature is dominated by the use of cognitive function (MMSE) as a basis to predict disease progression and to predict costs associated with care, and this limits the usefulness of such literature, given a growing evidence base showing that cognitive function (e.g. MMSE) alone may not be an accurate predictor of disease progression and cost of care.

Where the current literature has considered AD and the need for institutionalisation, there has been an absence of discussion and investigation into the important factors associated with the need for institutionalisation. Often the need for institutionalisation in patients with AD may be related to social circumstances and the availability of a carer to offer support, rather than progression of disease. The clinical trial literature is dominated by studies that have as an inclusion criterion the presence of a primary caregiver, and as such these trials may not reflect the full patient group for AD.

Strengths and limitations of the review

This review has a number of strengths which lead to a minimisation of bias. The review is independent of any vested interest and it brings together the evidence for the effectiveness of donepezil, rivastigmine, galantamine and memantine for AD, by the application of consistent methods of critical appraisal. It was guided by the principles for undertaking a systematic review and prior to undertaking the review, the methods were set out in a research protocol (Appendix 2). This protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods employed to undertake the different stages of the review. Finally, an advisory group has informed the review from its initiation, through the development of the research protocol and completion of the report.

There were certain limitations placed upon this review. Despite being guided by the principles for undertaking a systematic review, owing to time restrictions placed upon the review authors of references were not contacted for further details of their trials where data were lacking. As published papers are usually limited to 2500–5000 words it may be that some details of the trials are not published.

Implications for further research

The review has identified a wide range of subjective outcome measures among the included trials. The review has also noted that it is often unclear how statistically significant changes on these outcome measures translate into real benefit for the person with AD and for their carers. In many cases there is also uncertainty about the reliability and validity of the outcome measures used for these populations. Further research is required to answer a number of related questions (these may or may not need to be carried out separately for the population with mild to moderately severe AD and the population with moderately-severe to severe AD).

- To review the evidence base of the psychometric properties of key measures of global, cognitive, functional, behavioural and mood and QoL outcomes for the population of people with AD. In future research can be focused on using the most reliable and valid measures for this population.
- To investigate the correlation between statistical improvements on these key measures with perceived patient and carer benefit.
- To develop QoL measurement scales that are reliable and valid for the population with AD and their carers.

The review found only a few trials with a duration of follow-up of ≥12 months. The extent to which benefits on outcomes are maintained in patients over longer periods cannot be unequivocally assumed. It would be desirable to assess the effects of these drugs over long periods of follow-up; however, placebo-controlled randomised trials are now unlikely to be ethically acceptable. It may be possible to undertake a randomised 'withdrawal' trial after long-term treatment, randomising to either continued treatment or placebo.

The review identified only three randomised comparisons between the different cholinesterase inhibitors. These comparisons were small scale and offered very little to the evidence base regarding which intervention is most beneficial to patients. Larger, long-term RCTs comparing cholinesterase inhibitors in those with mild to moderately severe AD on outcomes such as cognition, function (ADLs), and behaviour and mood are required.

Few studies of memantine have been undertaken on patients with moderately severe to severe AD. Further RCTs comparing the effects of memantine with placebo in these populations on measures of function, behaviour and mood and carer QoL are required to inform any future up-date of the present review.

Research is required on the effectiveness of treatment on patient outcomes, such as health-related QoL, need for institutional care and delay in disease progression as defined by measures other than cognitive function alone.

Research on the prediction of disease progression, using a broad range of AD signs and symptoms (to include ADL and functional outcomes), is required. There appears to be an absence of data to model disease progression using multivariate analysis, including functional outcomes and measures of ADL, and initiatives to collect such data in an unbiased, methodologically rigorous and credible manner, should be encouraged. The current methods available to model disease progression over time are dominated by the use of cognitive function (MMSE), which is regarded as an insufficient marker of disease progression for AD.

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Contribution of authors

E Loveman (Senior Researcher), C Green (Senior Research Fellow) and A Clegg (Senior Research Fellow) prepared the protocol. E Payne (Information Scientist) searched the literature. E Loveman, C Green, J Kirby (Researcher), A Takeda (Researcher), J Picot (Researcher), and A Clegg prepared the inclusion criteria. E Loveman, C Green, J Kirby, A Takeda, J Picot and A Clegg were responsible for the data extraction. E Loveman, C Green, J Kirby, A Takeda, J Picot and A Clegg wrote the final report.

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References

1. Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*. Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review. *Health Technol Assess* 2001; **5**(1).
2. Ritchie K, Lovestone S. The dementias. *Lancet* 2002;**360**:1759–66.
3. Fratiglioni L, De Ronchi D, Aguero-Torres H. Worldwide prevalence and incidence of dementia. *Drugs Aging* 1999;**15**:365–75.
4. Rocca WA, Hofman A, Brayne C, Breteler MM, Clarke M, Copeland JR, *et al*. The prevalence of vascular dementia in Europe: facts and fragments from 1980–1990 studies. EURODEM-Prevalence Research Group. *Ann Neurol* 1991;**30**:817–24.
5. Andreasen N, Blennow K, Sjodin C, Winblad B, Svardsudd K. Prevalence and incidence of clinically diagnosed memory impairments in a geographically defined general population in Sweden. The Pitea Dementia Project. *Neuroepidemiology* 1999;**18**:144–55.
6. Kalaria R. Similarities between Alzheimer's disease and vascular dementia. *J Neurol Sci* 2002;**203**:29–34.
7. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan E. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; **34**:939–44.
8. Sandson TA, Price B. Diagnostic testing and dementia. *Neurol Clin* 1996;**14**:45–59.
9. Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, *et al*. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 2000;**54** (Suppl 5):Suppl-9.
10. Rocca WA. Frequency and distribution of Alzheimer's disease in Europe: a collaborative study of 1980–1990 prevalence findings. *Ann Neurol* 1991;**30**:381–90.
11. Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology* 1992;**42**:473–80.
12. Gold G, Giannakopoulos P, Montes-Paixao JC, Herrmann FR, Mulligan R, Michel JP, *et al*. Sensitivity and specificity of newly proposed clinical criteria for possible vascular dementia. *Neurology* 1997;**49**:690–4.
13. Zekry D, Hauw JJ, Gold G. Mixed dementia: epidemiology, diagnosis, and treatment. *J Am Geriatr Soc* 2002;**50**:1431–8.
14. Gearing M, Mirra SS, Hedreen JC, Sumi SM, Hansen LA, Heyman A. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part X. Neuropathology confirmation of the clinical diagnosis of Alzheimer's disease. *Neurology* 1995;**45**:t-6.
15. Hofman A, Rocca WA, Brayne C, Breteler MM, Clarke M, Cooper B, *et al*. The prevalence of dementia in Europe: a collaborative study of 1980–1990 findings. Eurodem Prevalence Research Group. *Int J Epidemiol* 1991;**20**:736–48.
16. Jagger C, Clarke M, Stone A. Predictors of survival with Alzheimer's disease: a community based study. *Psychol Med* 1995;**25**:171–7.
17. Walsh J, Welch G, Larson E. Survival of outpatients with Alzheimer-type dementia. *Ann Intern Med* 1990;**113**:429–34.
18. Pitt FA, Chilcott J, Golightly P, Sykes J, Whittingham M. *A review of the use of donepezil in the treatment of Alzheimer's disease*. Sheffield, Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield. Guidance Notes for Purchasers. Report No. 97/09; 1997.
19. Evans D, Smith LA, Scherr P, Albert M, Funkenstein HH, Hebert L. Risk of death from Alzheimer's disease in a community population of older persons. *Am J Epidemiol* 1991;**134**:403–12.
20. UK Government Actuary's Department. Population by age last birthday by single year of age; England and Wales 2002. URL: http://www.gad.gov.uk/Population/index.asp?v=Principal&y=2002&subYear=Continue. Accessed July 2004.
21. Copeland JR, McCracken CF, Dewey ME, Wilson KC, Doran M, Gilmore C, *et al*. Undifferentiated dementia, Alzheimer's disease and vascular dementia: age- and gender-related incidence in Liverpool. The MRC-ALPHA Study. *Br J Psychiatry* 1999;**175**:433–8.

22. Di Carlo A, Baldereschi M, Amaducci L, Lepore V, Bracco L, Maggi S, *et al*. Incidence of dementia, Alzheimer's disease, and vascular dementia in Italy. The ILSA Study. *J Am Geriatr Soc* 2002; **50**:41–8.

23. Kukull WA, Higdon R, Bowen JD, McCormick WC, Teri L, Schellenberg GD, *et al*. Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch Neurol* 2002;**59**:1737–46.

24. Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF, *et al*. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 2000;**54**(Suppl 5):Suppl-5.

25. Andersen K, Launer LJ, Dewey ME, Letenneur L, Ott A, Copeland JR, *et al*. Gender differences in the incidence of AD and vascular dementia: The EURODEM Studies. EURODEM Incidence Research Group. *Neurology* 1999;**53**:1992–7.

26. Holmes C, Cooper B, Levy R. Dementia known to mental health services: first findings of a case register for a defined elderly population. *Int J Geriatr Psychiatry* 2004;**10**:875–81.

27. Banerjee S. Services for older adults. In Thornicroft.G, Szmukler G, editors. *Textbook of community psychiatry*. London: Oxford University Press; 2001. pp. 381–96.

28. Neal M, Briggs M. Validation therapy for dementia. *Cochrane Database Syst Rev* 2003; (3):CD001394.

29. Grasel E, Wiltfang J, Kornhuber J. Non-drug therapies for dementia: an overview of the current situation with regard to proof of effectiveness. *Dement Geriatr Cogn Disord* 2003;**15**:115–25.

30. NICE Technology Appraisal Guidance – No. 19. *Guidance on the use of donepezil, rivastigmine and galantamine for the treatment of Alzheimer's disease*. London: NICE; 2003.

31. Lindesay J, Marudkar M, van Diepen E, Wilcock G. The second Leicester survey of memory clinics in the British Isles. *Int J Geriatr Psychiatry* 2002; **17**:41–7.

32. Department of Health. *National Service Framework for Older People*. London: Department of Health; 2001.

33. Phipps AJ, O'Brien JT. Memory clinics and clinical governance – a UK perspective. *Int J Geriatr Psychiatry* 2002;**17**:1128–32.

34. Marshall M. The challenge of looking after people with dementia (editorial). *BMJ* 2001;**323**:410–11.

35. Alzheimer's Disease Society. *Community care assessment*. URL: http://www.alzheimers.org.uk/After_diagnosis/PDF/418_communityAssess.pdf. Accessed 18 June 2004.

36. Ballard C, Fossey J, Chithramohan R, Howard R, Burns A, Thompson P, *et al*. Quality of care in private sector and the NHS facilities for people with dementia: cross sectional survey. *BMJ* 2001; **323**:426–7.

37. Becker RE. Therapy of the cognitive deficit in Alzheimer's disease: the cholinergic system. In Becker RE, Giacobini E, editors. *Cholinergic basis for Alzheimer therapy*. Boston; MD: Birkhauser; 1991.

38. CRD. *Undertaking systematic reviews of research on effectiveness. 4*. York: Centre for Reviews and Dissemination; 2001.

39. Drummond M, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**:275–83.

40. Alderson P, Green S, Higgins J, editors. *Cochrane reviewers' handbook 4.2.2 [updated March 2004]*. In *The Cochrane Library*, Issue 1. Chichester: John Wiley; 2004.

41. Gauthier S, Feldman H, Hecker J, Vellas B, Emir B, Subbiah P, *et al*. Functional, cognitive and behavioral effects of donepezil in patients with moderate Alzheimer's disease. *Curr Med Res Opin* 2002;**18**:347–54.

42. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E, *et al*. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease [published erratum appears in *Neurology* 2001;**57**:2153]. *Neurology* 2001;**57**:613–20.

43. AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* 2004;**363**:2105–15.

44. Homma A, Takeda M, Imai Y, Udaka F, Hasegawa K, Kameyama M, *et al*. Clinical efficacy and safety of donepezil on cognitive and global function in patients with Alzheimer's disease: a 24-week, multicenter, double-blind, placebo-controlled study in Japan. *Dement Geriatr Cogn Disord* 2000;**11**:299–313.

45. Krishnan KR, Charles HC, Doraiswamy PM, Mintzer J, Weisler R, Yu X, *et al*. Randomized, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. *Am J Psychiatry* 2003; **160**:2003–11.

46. Mohs RC, Doody RS, Morris JC, Ieni JR, Rogers SL, Perdomo CA, *et al*. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients [published erratum appears in *Neurology* 2001;**57**:1942]. *Neurology* 2001;**57**:481–8.

47. Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, *et al*. A 1-year, randomized,

placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001; **57**:489–95.

48. Nunez M, Hasselbalch S, Heun R, Kalisvaart CJ, Kozubski W, Sakka P, *et al*. Donepezil-treated Alzheimer's disease patients with apparent initial cognitive decline demonstrate significant benefits when therapy is continued: results from a randomised, placebo-controlled trial. Poster presented at the Second Annual Dementia Congress, 12–14 September 2003, Washington, DC, 2003.

49. Holmes C, Wilkinson D, Dean C, Vethanayagam S, Olivieri S, Langley A, *et al*. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer's disease. *Neurology* 2004; **63**:214–19.

50. Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Moller HJ, *et al*. The effects of donepezil in Alzheimer's disease – results from a multinational trial. *Dement Geriatr Cogn Disord* 1999;**10**:237–44.

51. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology* 1998;**50**:136–45.

52. Rogers SL, Doody RS, Mohs RC, Friedhoff LT, Alter M, Apter J, *et al*. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. *Arch Intern Med* 1998;**158**:1021–31.

53. Rogers SL, Friedhoff LT, Apter JT, Richter RW, Hartford JT, Walshe TM, *et al*. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicentre, randomized, double-blind, placebo-controlled trial. *Dementia* 1996;**7**:293–303.

54. Greenberg SM, Tennis MK, Brown LB, Gomez-Isla T, Hayden DL, Schoenfeld DA, *et al*. Donepezil therapy in clinical practice: a randomized crossover study. *Arch Neurol* 2000; **57**(9):1380.

55. Seltzer B, *et al*. **[Commercial confidential information removed]** A 24-week, multicenter, randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil hydrochloride (E2020) in patients with early Alzheimer's disease. Industry submission, 2004.

56. Wimo A, Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, *et al*. An economic evaluation of donepezil in mild to moderate Alzheimer's disease: results of a 1-year, double-blind, randomized trial [published erratum appears in *Dement Geriatr Cogn Disord*. 2003;**16**:102]. *Dement Geriatr Cogn Disord* 2003; **15**:44–54.

57. Corey-Bloom J, Anand R, Veach J. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *Int J Geriatr Psychopharmacol* 1998;**1**:55–65.

58. Rösler M, Anand R, Cicin SA, Gauthier S, Agid Y, Dal Bianco P, *et al*. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ* 1999;**318**:633–40.

59. Agid Y, Dubois B, Anand R, Gharabawi G. Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. *Curr Ther Res Clin Exp* 1998;**59**:837–45.

60. Forette F, Anand R, Gharabawi G. A phase II study in patients with Alzheimer's disease to assess the preliminary efficacy and maximum tolerated dose of rivastigmine. *Eur J Neurol* 1999;**6**:423–9.

61. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD. A 6-month randomised, placebo-controlled trial with a 6-month extension. *Neurology* 2000;**54**:2261–8.

62. Rockwood K, Mintzer J, Truyen L, Wessel T, Wilkinson D. Effects of a flexible galantamine dose in Alzheimer's disease: a randomised, controlled trial. *J Neurol Neurosurg Psychiatry* 2001;**71**:589–95.

63. Tariot P, Solomon PR, Morris J, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomised, placebo-controlled trial of galantamine in AD. *Neurology* 2000;**54**:2269–76.

64. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: Multicentre randomised controlled trial. *BMJ* 2000;**321**:1445–9.

65. Wilkinson D, Murray J. Galantamine: a randomized, double-blind, dose comparison in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2001;**16**:852–7.

66. Wilkinson D, Lilienfeld S, Truyen L. Galantamine improves activities of daily living in patients with alzheimer's disease: a 3 month placebo-controlled study. In *Proceedings of the Sixth International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy*, Stockholm, 5–8 April 2000. p. 233.

67. Cummings JL, Schneider L, Tariot PN, Kershaw PR, Yuan W. Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. *Am J Psychiatry* 2004;**161**:532–8.

68. Fuschillo C, La Pia S, Campana F, Pinto A, De Simone L. Cognitive deficits in Alzheimer's disease: Treatment with acetylcholinesterase inhibitor agents. *Arch Gerontol Geriatr* 2001;**7**: 151–8.

69. Wilkinson DG, Passmore AP, Bullock R, Hopker SW, Smith R, Potocnik FC, *et al*. A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. *Int J Clin Pract* 2002;**56**:441–6.

70. Jones RW, Soininen H, Hager K, Aarsland D, Passmore P, Murthy A, *et al*. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;**1**:58–67.

71. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I, *et al*. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* 2004;**291**:317–24.

72. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ, *et al*. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med* 2003;**348**:1333–41.

73. Larson E. Galantamine improved cognition and global functioning in vascular dementia or Alzheimer disease with cerebrovascular disease. *ACP J Club* 2002;**137**(3):102.

74. Wolfson C, Moride Y, Perrault A, Momoli F, Demers L, Oremus M. *Drug treatments for Alzheimer's disease: 1. A comparative analysis of clinical trials*. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2000.

75. Livingston G, Katona C. How useful are cholinesterase inhibitors in the treatment of Alzheimer's disease: a number needed to treat analysis. *Int J Geriatr Psychiatry* 2000;**15**:203–7.

76. Birks JS, Harvey R. Donepezil for dementia due to Alzheimer's disease. In *The Cochrane Library*, Issue 1. Chichester: John Wiley; 2004.

77. Birks J, Grimley EJ, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. In *The Cochrane Library*, Issue 1, Chichester: John Wiley; 2004.

78. Wolfson C, Oremus M, Shukla V, Momoli F, Demers L, Perrault A, *et al*. Donepezil and rivastigmine in the treatment of Alzheimer's disease: a best-evidence synthesis of the published data on their efficacy and cost-effectiveness. *Clin Ther* 2002;**24**:862–86.

79. Olin J, Schneider L. Galantamine for Alzheimer's disease. *Cochrane Database Syst Rev* 2001;(4). Chichester: John Wiley.

80. Areosa SA, Sherriff F. Memantine for dementia. In *The Cochrane Library*, Issue 1. Chichester: John Wiley; 2004.

81. Stein K. *Donepezil in the treatment of mild to moderate senile dementia of the Alzheimer type (SDAT)*. Development and Evaluation Committee Report, 69. Bristol: NHS Executive South and West; 1997.

82. Stewart A, Phillips R, Dempsey G. Pharmacotherapy for people with Alzheimer's disease: a Markov-cycle evaluation of five years' therapy using donepezil. *Int J Geriatr Psychiatry* 1998;**13**:445–53.

83. Lanctôt K, Oh P, Risebrough N. Cost–benefit analysis of cholinesterase inhibitors (ChEI) in Alzheimer's disease (AD). In *One-hundredth Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, 18–20 March 1999*. San Antonia, TX: 1999;(2):169.

84. Jönsson L, Lindgren P, Wimo A, Jönsson B, Winblad B. The cost-effectiveness of donepezil therapy in Swedish patients with Alzheimer's disease: a Markov model. *Clin Ther* 1999; **21**:1230–40.

85. O'Brien BJ, Goeree R, Hux M, Iskedjian M, Blackhouse G, Gagnon M, *et al*. Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada. *J Am Geriatr Soc* 1999;**47**:570–8.

86. Neumann PJ, Hermann RC, Kuntz KM, Araki SS, Duff SB, Leon J, *et al*. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. *Neurology* 1999;**52**:1138–45.

87. Ikeda S, Yamada Y, Ikegami N. Economic evaluation of donepezil treatment for Alzheimer's disease in Japan. *Dement Geriatr Cogn Disord* 2002; **13**:33–9.

88. Sobolewski M, Kuzniar J, Splawinski J. Is donepezil cost-effective in the treatment of Alzheimer's disease? *Neurobiol Aging* 2002;**23**:368.

89. Fagnani F, Lafuma A, Pechevis M, Rigaud AS, Traykov L, Seux ML, *et al*. Donepezil for the treatment of mild to moderate Alzheimer's disease in France: economic implications. *Dement Geriatr Cogn Disord* 2003;**17**:5–13.

90. Stein K. *Rivastigmine (Exelon) in the treatment of senile dementia of the Alzheimer type (SDAT)*. Development and Evaluation Committee Report, 89. Bristol: NHS Executive South and West; 1998.

91. Fenn P, Gray A. Estimating long term cost savings from treatment of Alzheimer's disease: a modelling approach. *Pharmacoeconomics* 1999; **16**:165–74.

92. Hauber AB, Gnanasakthy A, Snyder EH, Bala MV, Richter A, Mauskopf JA. Potential savings in the cost of caring for Alzheimer's disease – treatment with rivastigmine. *Pharmacoeconomics* 2000;**17**:351–60.

93. Hauber AB, Gnanasakthy A, Mauskopf JA. Savings in the cost of caring for patients with Alzheimer's disease in Canada: an analysis of treatment with rivastigmine. *Clin Ther* 2000;**22**:439–51.

94. Brooks E, Deal L. The effect of rivastigmine on the direct and indirect costs of Alzheimer's disease. *Value in Health* 2000;**3**:79.

95. Getsios D, Caro JJ, Caro G, Ishak K, AHEAD Study Group. Assessment of health economics in Alzheimer's disease (AHEAD): galantamine treatment in Canada. *Neurology* 2001;**57**:972–8.

96. Garfield FB, Getsios D, Caro JJ, Wimo A, Winblad B. Assessment of Health Economics in Alzheimer's Disease (AHEAD): treatment with galantamine in Sweden. *Pharmacoeconomics* 2002; **20**:629–37.

97. Caro JJ, Salas M, Ward A, Getsios D, Mehnert A. Economic analysis of galantamine, a cholinesterase inhibitor, in the treatment of patients with mild to moderate Alzheimer's disease in The Netherlands. *Dement Geriatr Cogn Disord* 2002;**14**:84–9.

98. Migliaccio-Walle K, Getsios D, Caro JJ, Ishak KJ, O'Brien JA, Papadopoulos G, *et al*. Economic evaluation of galantamine in the treatment of mild to moderate Alzheimer's disease in the United States. *Clin Ther* 2003;**25**:1806–25.

99. Ward A, Caro JJ, Getsios D, Ishak K, O'Brien J, Bullock R, *et al*. Assessment of health economics in Alzheimer's disease (AHEAD): treatment with galantamine in the UK. *Int J Geriatr Psychiatry* 2003;**18**:740–7.

100. Guilhaume C. Cost effectiveness of memantine in the treatment of moderately severe and severe Alzheimer's disease in Finland. *Eur J Neurol* 2003; **10**(Suppl 1):159–60.

101. Launois R, Guilhame C, Francois C, Maehlum E. Cost effectiveness of memantine in the treatment of moderately severe and severe alzheimer's disease in Norway. International Conference on Alzheimer's and Parkinson's Diseases. Seville; 2003.

102. Antonanzas F, Badenas J, Francois C, Guilhaume C. Cost effectiveness of memantine in the treatment of moderately severe and severe Alzheimer's disease in Spain. *Value Health* 2003; **6**:765.

103. François C, Sintonen H, Sulkava R. The cost-effectiveness of memantine in moderately severe to severe Alzheimer's disease. A Markov model in Finland. *Clin Drug Invest* 2004;**27**:373–84.

104. Jones R, McCrone P, Guilhaume C. Cost effectiveness of memantine in Alzheimer's disease: an analysis based on a probabilistic Markov model from a UK perspective. *Drugs Aging* 2004; **21**:607–20.

105. Foster RH, Plosker GL. Donepezil. Pharmacoeconomic implications of therapy. *Pharmacoeconomics* 1999;**16**:99–114.

106. Lamb HM, Goa KL. Rivastigmine – a pharmacoeconomic review of its use in Alzheimer's disease. *Pharmacoeconomics* 2001;**19**:303–18.

107. Lyseng-Williamson K, Plosker GL. Galantamine: a pharmacoeconomic review of its use in Alzheimer's disease. *Pharmacoeconomics* 2002;**20**:919–42.

108. Shukla VK, Otten N, Coyle D. *Drug treatments for Alzheimer's disease. III. A review of pharmacoeconomic evaluations*. Technology Report 11. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2000. pp. 1–39.

109. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*. A review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technology Assess* 2004;**8**(36).

110. Neumann PJ, Kuntz KM, Leon J, Araki SS, Hermann RC, Hsu MA, *et al*. Health utilities in Alzheimer's disease: a cross-sectional study of patients and caregivers. *Med Care* 1999;**37**:27–32.

111. Ely M, Melzer D, Opit L, Brayne C. Estimating the number and characteristics of people with cognitive disability in local populations. *Res Policy Planning* 1996;**14**(2):13–18.

112. Burns A, Forstl H. The Institute of Psychiatry Alzheimer's disease cohort: part I – clinical observations. *Int J Geriatr Psychiatry* 1996;**11**:309–20.

113. Burns A, Forstl H. The Institute of Psychiatry Alzheimer's disease cohort: part II – clinicopathological observations. *Int J Geriatr Psychiatry* 1996;**11**:321–7.

114. Hogan DB, Thierer DE, Ebly EM, Parhad IM. Progression and outcome of patients in a Canadian dementia clinic. *Can J Neurol Sci* 1994; **21**:331–8.

115. Helmer C, Letenneur L, Dartigues J. Longévité des déments. Démences et longévité. Paris: Fondation Nationale de Gérontologie; 1997. pp. 111–22 (in French).

116. Letenneur L, Dequae L, Jacqmin H, Nuissier J, Decamps A, Barberger-Gateau P, *et al*. Prevalence of dementia in Gironde (France). *Rev Epidemiol Santé Publ* 1993;**41**:139–45 (in French).

117. Obadia Y, Rotily M, Degrand-Guillaud A, Guelain J, Ceccaldi M, Severo C, *et al*. The PREMAP Study: prevalence and risk factors of dementia and clinically diagnosed Alzheimer's disease in Provence, France. Prevalence of Alzheimer's Disease in Provence. *Eur J Epidemiol* 1997;**13**:247–53.

118. Kavanagh S, Schneider J, Knapp M, Beecham J, Netten A. Elderly people with cognitive impairment: costing possible changes in the balance of care. *Health Soc Care Commun* 1993; **1**:69–80.

119. Schneider J, Kavanagh S, Knapp M, Beecham J, Netten A. Elderly people with advanced cognitive impairment in England: resource use and costs. *Ageing Soc* 1993;**13**:27–50.

120. Kavanagh S, Schneider J, Knapp M, Beecham J, Netten A. Elderly people with dementia: cost effectiveness and balance of care. In Knapp M, editor. *The economic evaluation of mental health care*. Aldershot: Arena; 1995. pp. 125–56.

121. Stewart A. *Costs of care for people with dementia aged 75 and over*. Discussion paper 1303/2. University of Kent, Canterbury: PSSRU; 1997.

122. Wolstenholme J, Fenn P, Gray A, Keene J, Jacoby R, Hope T. Estimating the relationship between disease progression and cost of care in dementia. *Br J Psychiatry* 2002;**181**:36–42.

123. Bowie P, Branton T, Holmes J. Should the mini mental state examination be used to monitor dementia treatments? *Lancet* 1999;**354**:1527–8.

124. Davey RJ, Jamieson S. The validity of using the mini mental state examination in NICE dementia guidelines. *J Neurol Neurosurg Psychiatry* 2004; **75**:343–4.

125. Tombaugh TN, Mcintyre NJ. The mini-mental-state-examination – a comprehensive review. *J Am Geriatr Soc* 1992;**40**:922–35.

126. Gray A, Fenn P. Alzheimer's disease: the burden of the illness in England. *Health Trends* 1993;**25**:31–7.

127. *Monitoring alzheimer's disease in nursing homes*. 046/911. London: Taylor Nelson AGB; 1997.

128. Mendiondo MS, Ashford JW, Kryscio RJ, Schmitt FA. Modelling mini mental state examination changes in Alzheimer's disease. *Stat Med* 2000; **19**:1607–16.

129. Martin DC, Miller JK, Kapoor W, Arena VC, Boller F. A controlled study of survival with dementia [published erratum appears in *Arch Neurol* 1988;**45**:619]. *Arch Neurol* 1987;**44**:1122–6.

130. Netten A, Darton R, Bebbington A, Forder J, Brown P, Mummery K. Residential and nursing home care of elderly people with cognitive impairment: prevalence, mortality and costs. *Aging Ment Health* 2001;**5**:14–22.

131. Caro JJ, Getsios D, Migliaccio-Walle K, Raggio G, Ward A. Assessment of health economics in Alzheimer's disease (AHEAD) based on need for full-time care. *Neurology* 2001;**57**:964–71.

132. Stern Y, Tang MX, Albert MS, Brandt J, Jacobs DM, Bell K, *et al*. Predicting time to nursing home care and death in individuals with Alzheimer disease. *JAMA* 1997;**277**:806–12.

133. Richards M, Marder K, Bell K, Dooneief G, Mayeux R, Stern Y. Interrater reliability of extrapyramidal signs in a group assessed for dementia. *Arch Neurol* 1991;**48**:1147–9.

134. Martin J, Meltzer H, Elliot D. *The prevalence of disability among adults: OPCS surveys of disability in Great Britain Report 1*. London: HMSO; 1988.

135. Doraiswamy PM, Bieber F, Kaiser L, Krishnan KR, Reuning-Scherer J, Gulanski B. The Alzheimer's Disease Assessment Scale: patterns and predictors of baseline cognitive performance in multicenter Alzheimer's disease trials. *Neurology* 1997; **48**:1511–17.

136. Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*. Clinical and cost-effectiveness of donepezil, rivastigmine, and galantamine for Alzheimer's disease. A systematic review. *Int J Technol Assess Health Care* 2002; **18**:497–507.

137. Husereau D, Wolfson C, Shukla V. Drug treatments for Alzheimer's disease: efficacy, outcome measurements and cost effectiveness. *Technol Overview* 2001;(4).

138. Small GW, Donohue JA, Brooks RL. An economic evaluation of donepezil in the treatment of Alzheimer's disease. *Clin Ther* 1998;**20**:838–50.

139. Fillit H, Gutterman EM, Lewis B. Donepezil use in managed Medicare: effect on health care costs and utilization. *Clin Ther* 1999;**21**:2173–85.

140. Lanctot K, Risebrough N, I. Factors affecting the economic attractiveness of cognitive enhancers in Alzheimer's disease. Annual Meeting of the Canadian Society for Clinical Investigation, the Royal College of Physicians and Surgeons of Canada and Participating Societies Toronto, Ontario, Canada, September 1998. *Clin Invest Med* 1998;**24–27**(Suppl):S17.

141. Tariot P, Federoff HJ. Current treatment for Alzheimer disease and future prospects. *Alzheimer Dis Assoc Disord* 2003;**17**(Suppl 4):S105–113.

142. Mackell JA, Ferris SH, Mohs R, Schneider L, Galasko D, Whitehouse P, *et al*. Multicenter evaluation of new instruments for Alzheimer's disease clinical trials: summary of results. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* 1997;**11**:Suppl-9.

143. Rahkonen T, Eloniemi-Sulkava U, Rissanen S, Vatanen A, Viramo P, Sulkava R. Dementia with Lewy bodies according to the consensus criteria in a general population aged 75 years or older. *J Neurol Neurosurg Psychiatry* 2003;**74**:720–4.

144. Paton J, Johnston K, Katona C, Livingston G. What causes problems in Alzheimer's disease: attributions by caregivers. *Int J Geriatr Psychiatry* in press.

145. Kronborg Andersen C, Sogaard J, Hansen E, Kragh-Sorensen A, Hastrup L, Andersen J, *et al*. The cost of dementia in Denmark: the Odense Study. *Dement Geriatr Cogn Disord* 1999;**10**:295–304.

146. Livingston G, Katona C, Roch B, Guilhame C, Rive B. A dependency model for patients with Alzheimer's disease: its validation and relationship to the costs of care – the LASER-AD Study. *Curr Med Res Opin* 2004;**S7**:1007–16.

147. Wimo A, Winblad B, Stoffler A, Wirth Y, Mobius HJ. Resource utilisation and cost analysis

of memantine in patients with moderate to severe Alzheimer's disease. *Pharmacoeconomics* 2003; **21**:327–40.

148. Kronborg Andersen C, Nielsen H, Lolk A, Andersen J, Becker I, Kragh-Sorensen P. Incidence of very mild to severe dementia and Alzheimer's disease in Denmark: the Odense Study. *Neurology* 1999;**52**:85–90.

149. Bloom BS, de Pouvourville N, Straus WL. Cost of illness of Alzheimer's disease: how useful are current estimates? *Gerontologist* 2003;**43**:158–64.

150. *British National Formulary*, No. 49 (March). London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; 2005.

151. Department of Health. *NHS Reference Costs 2002*. URL: http://www.doh.gov.uk/nhsexec/refcosts.htm

152. O'Shea E, O'Reilly S. The economic and social cost of dementia in Ireland. *Int J Geriatr Psychiatry* 2000;**15**:208–18.

153. Stewart A. *Donepezil in the treatment of people with Alzheimer's disease: a pilot Markov approach*. Discussion paper 1324. PSSRU; 1997.

154. Blackwell J, O'Shea E, Moane G, Murray P. *Care provision and cost measurement: dependent elderly people at home and in geriatric hospitals*. Dublin: Economic and Social Research Institute; 1992.

155. Hope T, Keene J, Fairburn C, McShane R, Jacoby R. Behaviour changes in dementia. 2: Are there behavioural syndromes? *Int J Geriatr Psychiatry* 1997;**12**:1074–8.

156. Hope T, Keene J, Gedling K, Cooper S, Fairburn C, Jacoby R. Behaviour changes in dementia. 1: Point of entry data of a prospective study. *Int J Geriatr Psychiatry* 1997;**12**:1062–73.

157. Morris JN, Fries BE, Mehr DR, Hawes C, Phillips C, Mor V, *et al*. MDS Cognitive Performance Scale. *J Gerontol* 1994;**49**:M174–82.

158. Souêtre E, Thwaites RM, Yeardley HL. Economic impact of Alzheimer's disease in the United Kingdom. Cost of care and disease severity for non-institutionalised patients with Alzheimer's disease. *Br J Psychiatry* 1999;**174**:51–5.

159. NHS funded nursing care in nursing homes: what it means for you. URL: www.doh.gov.uk/joint/unit/freenursingcare/residentscarersguide.pdf. Accessed 2004.

160. Alzheimers Society. *Paying home care fees*. Information Sheet. London: Alzheimers Society; 2004.

161. Whitehouse P. Measurements of quality of life in dementia. In Wimo A, Jonsson B, Karlsson G, Winblad B, editors. *Health economics of dementia*. Chichester: John Wiley; 1998. pp. 403–17.

162. Walker MD, Salek SS, Bayer AJ. A review of quality of life in Alzheimer's disease. Part 1: Issues in assessing disease impact. *Pharmacoeconomics* 1998; **14**:499–530.

163. Leon J, Neumann PJ, Hermann RC, Hsu M-A, Cummings JL, Doraiswamy PM, *et al*. Health-related quality-of-life and service utilization in Alzheimer's disease: a cross-sectional study. *Am J Alzheimer's Dis* 2000;**15**:94–108.

164. Neumann PJ, Sandberg EA, Araki SS, Kuntz KM, Feeny D, Weinstein MC. A comparison of HUI2 and HUI3 utility scores in Alzheimer's disease. *Med Decis Making* 2000;**20**:413–22.

165. Torrance GW, Feeny DH, Furlon WJ, Barr RD, Zhang Y, Wang Q. Multi-attribute preference functions for a comprehensive health status classification system: Health Utilities Index Mark 2. *Med Care* 1996;**24**:702–22.

166. Neumann PJ. Measuring QALYS in dementia. In Wimo A, Jonsson B, Karlsson G, Winblad B, editors. *Health economics of dementia*. Chichester: John Wiley; 1998. pp. 359–70.

167. Zimmerman SJ, Magaziner J. Methological issues in measuring the functional status of cognitively impaired nursing home residents: the use of proxies and performance based measures. *Alzheimer Dis Assoc Disord* 1994;**8**(Suppl 1):281–90.

168. Kerner DN, Patterson TL, Grant I, Kaplan RM. Validity of the quality of well-being scale for patients with Alzheimer's disease. *J Aging Health* 1998;**10**:44–61.

169. Kaplan RM, Anderson JP. A general health policy model: update and applications. *Health Serv Res* 1988;**23**:203–35.

170. Sano M, Albert SM, Tractenberg R, Schittini M. Developing utilities: quantifying quality of life for stages of Alzheimer's disease as measured by the Clinical Dementia Rating. *J Ment Health Aging* 1999;**5**:59–68.

171. Dodge HH, Shen C, Pandav R, DeKosky ST, Ganguli M. Functional transitions and active life expectancy associated with Alzheimer disease. *Arch Neurol* 2003;**60**:253–9.

172. Burns A, Lewis G, Jacoby R, Levy R. Factors affecting survival in Alzheimer's disease. *Psychol Med* 1991;**21**:363–70.

173. Newcomer R, Covinsky KE, Clay T, Yaffe K. Predicting 12-month mortality for persons with dementia. *J Gerontol B Psychol Sci Soc Sci* 2003; **58**:S187–98.

174. Hui JS, Wilson RS, Bennett DA, Bienias JL, Gilley DW, Evans DA. Rate of cognitive decline and mortality in Alzheimer's disease. *Neurology* 2003;**61**:1356–61.

175. Lapane KL, Gambassi G, Landi F, Sgadari A, Mor V, Bernabei R. Gender differences in predictors of mortality in nursing home residents with AD. *Neurology* 2001;**56**:650–4.

176. Aneshensel CS, Pearlin LI, Levy-Storms L, Schuler RH. The transition from home to nursing home mortality among people with dementia. *J Gerontol B Psychol Sci Soc Sci* 2000;**55**:S152–62.

177. Mitchell SL, Kiely DK, Hamel MB, Park PS, Morris JN, Fries BE. Estimating prognosis for nursing home residents with advanced dementia. *JAMA* 2004;**291**:2734–40.

178. Clark CM, Sheppard L, Fillenbaum G, Galasko D, Morris JC, Koss E, *et al*. Variability in annual mini-mental state examination score in patients with probably Alzheimer's disease. *Arch Neurol* 1999; **56**:857–62.

179. Neumann PJ, Araki SS, Arcelus A, Longo A, Papadopoulos G, Kosik KS, *et al*. Measuring Alzheimer's disease progression with transition probabilities: estimates from CERAD. *Neurology* 2001;**57**:957–64.

180. Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, *et al*. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* 1989; **39**:1159–65.

181. Mendiondo MS, Kryscio RJ, Schmitt FA. Models of progression in AD: predicting disability and costs [comment]. *Neurology* 2001;**57**:943–4.

182. BBC News. *Britons ignoring dementia signs*. 2004.

183. Wilkinson D, Stave C, Keohane D, Vincenzino O. The role of general practitioners in the diagnosis and treatment of Alzheimer's disease: a multinational survey. *J Int Med Res* 2004;**32**:149–59.

184. Williams A. *The measurement and valuation of health. A chronicle*. Discussion Paper 136. York: University of York Centre for Health Economics; 1995.

185. Kavanagh S, Knapp M. Costs and cognitive disability: modelling the underlying associations. *Br J Psychiatry* 2002;**180**:120–5.

186. Kavanagh S, Knapp M. Cognitive disability and direct care costs for elderly people. *Br J Psychiatry* 1999;**174**:539–46.

187. Neumann, Hermann RC, Weinstein MC. Measuring QALYs in dementia. In Wimo A, Jonsson B, Karlsson G, Winblad B, editors. *Health economics of dementia*. Chichester: John Wiley; 1998.

188. McDaid D. Estimating the costs of informal care for people with Alzheimer's disease: methodological and practical challenges. *Int J Geriatr Psychiatry* 2001;**16**:400–5.

189. Department of Health. *Prescription cost analysis 2003*. URL: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsStatistics/. Accessed 2004.

190. The European Agency for the Evaluation of Medicinal Products. *Note for guidance on medicinal products in the treatment of Alzheimer's disease*. London: CPMP; 1997.

191. Holmes C, Lovestone S. Long-term cognitive and functional decline in late onset Alzheimer's disease: therapeutic implications. *Age Ageing* 2003; **32**:200–4.

192. Wilcock G, Howe I, Coles H, Lilienfeld S, Truyen L, Zhu Y, *et al*. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. *Drugs Aging* 2003;**20**:777–89.

193. Jonsson L, Lindgren P, Wimo A, Jonsson B, Winblad B. Costs of mini mental state examination-related cognitive impairment. *Pharmacoeconomics* 1999;**16**:409–16.

194. *Statistic yearbook*. Stockholm: Statistica Centralbyrån; 1995.

195. Canadian study of health and aging: study methods and prevalence of dementia. *CMAJ* 1994; **150**:899–913.

196. Rice DP, Fox PJ, Max W, Webber PA, Lindeman DA, Hauck WW, *et al*. The economic burden of Alzheimer's disease care. *Health Aff (Millwood)* 1993;**12**:164–76.

197. Ernst RL, Hay JW, Fenn C, Tinklenberg J, Yesavage JA. Cognitive function and the costs of Alzheimer disease: an exploratory study. *Arch Neurol* 1997;**54**:687–93.

198. Hux MJ, O'Brien BJ, Iskedjian M, Goeree R, Gagnon M, Gauthier S. Relation between severity of Alzheimer's disease and costs of caring. *CMAJ* 1998;**159**:457–65.

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The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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