NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease

(Review of NICE technology appraisal guidance 111)

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees and commentators' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

1 Background

1.1 The condition

Dementia is a chronic progressive mental disorder that adversely affects higher cortical functions including memory, thinking and orientation. Alzheimer's disease is the most common form of dementia. It is a degenerative cerebral disease with characteristic neuropathological and neurochemical features.

Alzheimer's disease is usually insidious in onset and develops slowly but steadily over several years. It affects older people predominantly. Progression varies according to the individual but is characterised by deterioration in cognition (thinking, conceiving and reasoning), functional ability (activities of daily living) and disturbance in behaviour and mood. People might have a general deterioration in the ability to do everyday activities, such as shopping or managing finances, to socialise and to recognise people and places. Communication may become a problem as people find it more difficult to find words and recall names. In later stages of disease, physical problems can include problems eating, swallowing, incontinence and unsettled and unsettling behaviour. Alzheimer's disease may also be associated with loss of

confidence and feelings of fear, confusion, apathy, stigma and depression. The median survival for people with Alzheimer's disease from onset has been estimated as 7 years, although survival figures vary and depend on how they are measured, comorbidities, age and gender.

People who care for a person with Alzheimer's disease, including friends and family, are also affected. In particular, several consultee submissions (from Alzheimer's Society, the British Geriatrics Society and the Royal College of Psychiatrists) have noted the impact of behavioural symptoms on carers, which is often the reason cited for the person with Alzheimer's disease going into full-time residential care.

Several methods are available to assess the severity of Alzheimer's disease for different outcomes. Mini Mental State Examination (MMSE) score, for example, denotes the severity of cognitive impairment in some people as follows:

- mild Alzheimer's disease: MMSE 21–26
- moderate Alzheimer's disease: MMSE 10–20
  - moderately severe Alzheimer's disease: MMSE 10–14
- severe Alzheimer's disease: MMSE less than 10.

However, clinical practice uses various measures to assess disease severity, often along with clinically based assessments such as biographical interview. Other instruments for measuring cognition include the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) and Severe Impairment Battery (SIB). Instruments for assessing function include the Progressive Deterioration Scale (PDS), Disability Assessment for Dementia (DAD), Alzheimer's Disease Cooperative Studies Activities of Daily Living (ADCS/ADL) and Instrumental Activities of Daily Living (IADL) scale. The main instrument for assessing behaviour is the neuropsychiatric inventory (NPI). Instruments for assessing global outcomes include the Global Deterioration Scale (GDS), Clinical Global Impression of Change, the Clinician's Interview-

Based Impression of Change (CIBIC), CIBIC-plus and the Gottfries-Brane-Steen scale.

Population data (2005) for England and Wales indicate 380,000 people have Alzheimer's disease. The UK incidence for Alzheimer's disease in people over the age of 65 years is estimated as 4.9 per 1000 person-years. In people with Alzheimer's disease, 50–64% are estimated to have mild to moderately severe disease, and approximately 50% have moderately severe to severe disease.

1.2 Current management

People with mild Alzheimer's disease are sometimes able to cope without assistance, but as the disease progresses, all eventually require the aid of carers, and about half need residential care. People with Azheimer's disease usually present to their GP with memory problems. Some people also visit specialist clinics.

The aims of treatment include managing symptoms, slowing progression, maintaining abilities in early disease and improving quality of life. There is no cure for Alzheimer's disease. Management of Alzheimer's disease, addressed by 'Dementia: supporting people with dementia and their carers in health and social care' (NICE clinical guideline 42), involves treating cognitive, behavioural and psychological symptoms. Acetylcholinesterase (AChE) inhibitors and memantine are the only available pharmacological treatments specifically for Alzheimer's disease. Risperidone, an atypical antipsychotic, is licensed 'for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others'. Non-pharmacological treatment is social support and increasing assistance with day-to-day activities. These include information and education, carer support groups, community dementia teams, home nursing and personal care, community services such as meals-on-wheels, befriending services, day centres, respite care and care homes.

'Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (amended)' (NICE technology appraisal guidance 111), initially published in 2006 and updated in 2007 and 2009, recommends the three AChE inhibitors donepezil, galantamine and rivastigmine as options in the management of patients with Alzheimer's disease of moderate severity only (for people with a MMSE score of between 10 and 20 points). Memantine is not recommended as a treatment option for people with moderately severe to severe Alzheimer's disease except as part of well designed clinical studies. See Appendix B for the full recommendations from NICE technology appraisal guidance 111.

Consultee submissions from Alzheimer's Society, the British Geriatrics Society and the Royal College of Psychiatrists note that behavioural symptoms are common and can occur in over 50% of patients with severe Alzheimer's disease. They also note that antipsychotics (such as risperidone, which is licensed for short term use, and olanzapine) are often used for the first-line treatment of behavioural symptoms, although they are associated with a higher risk of stroke, cerebrovascular events and mortality in older dementia patients. The National Dementia Strategy, therefore, highlighted the need to reduce antipsychotic prescription in people with dementia.

The submission from Alzheimer's Society notes that drug treatments are not effective in all people with Alzheimer's disease but that for others the drugs appear to delay disease progression, and reduce confusion and anxiety, which improves patients' and carers' quality of life and relationships.

Data from a survey conducted in 2004 submitted by Alzheimer's Society showed 2672 out of 4060 people with Alzheimer's disease or their carers had experience of donepezil, galantamine, rivastigmine or memantine and 761 people were receiving one of the four drugs at the time of the survey. Of those who had experience of one of the four drugs, 77% had tried donepezil, 18% had tried rivastigmine, 18% had tried galantamine and 14% had tried memantine. The drugs were mainly prescribed on the NHS, but 46% of those on memantine had a private prescription.

2 The technologies

Table 1 Summary description of technologies

Drug name	Dose	Acquisition cost – tablets (BNF edition 59)
Donepezil	Initially 5 mg once daily at bedtime, increased if necessary after one month to a maximum of 10 mg daily	**Tablets:** 5 mg, net price 28-tab pack = £63.54; 10 mg, 28-tab pack = £89.06. **Orodispersible tablets**: 5 mg, net price 28-tab pack = £63.54; 10 mg, 28-tab pack = £89.06.
Galantamine	Initially 4 mg twice daily for 4 weeks increased to 8 mg twice daily for 4 weeks; maintenance 8–12 mg twice daily	**Tablets:** 8 mg, net price 56-tab pack = £68.32; 12 mg 56-tab pack = £84.00. **Oral solution**: 4 mg/ml, net price 100 ml = £120.00. **Capsules:** 8 mg, net price 28-cap pack = £51.88; 16 mg, 28-cap pack = £64.90; 24 mg, 28-cap pack = £79.80.
Rivastigmine	Dose Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily at intervals of at least 2 weeks according to response and tolerance; usual range 3–6 mg twice daily; maximum 6 mg twice daily	**Capsules:** 1.5 mg net price 28-cap pack = £33.25, 56-cap pack = £66.51; 3 mg, 28-cap pack = £33.25, 56-cap pack = £66.51; 4.5 mg, 28-cap pack = £33.25, 56-cap pack = £66.51; 6 mg, 28-cap pack = £33.25, 56-cap pack = £66.51. **Oral solution**: 2 mg/ml, net price 120 ml = £99.14. **Patches:** 4.6 mg/24 hours, net price 30 = £77.97; 9.5 mg/24 hours, 30 = £77.97.
Memantine	Initially 5 mg once daily, increased in steps of 5 mg at weekly intervals; maximum 20 mg daily	**Tablets:** 10 mg, net price 28-tab pack = £34.50, 56-tab pack = £69.01, 112-tab pack = £138.01; 20 mg, 28-tab pack = £69.01; treatment initiation pack, 7 × 5 mg, 7 × 10 mg, 7 × 15 mg, and 7 × 20 mg = £43.13 **Oral drops:** 10 mg/g, net price 50 g = £61.61, 100 g = £123.23
Costs may vary in different settings because of negotiated procurement discounts. BNF = British National Formulary		

AChE inhibitors: donepezil, galantamine, rivastigmine

Donepezil (Aricept, Eisai/Pfizer), rivastigmine (Exelon, Novartis), and galantamine (Reminyl, Shire) are AChE inhibitors, which work by increasing the concentration of acetylcholine at sites of neurotransmission. Galantamine also modulates activity at nicotinic receptors. Donepezil, rivastigmine and galantamine have marketing authorisations in the UK for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

Common undesirable effects of AChE inhibitors affect the gastrointestinal tract and include nausea and vomiting. These effects are dose related and although they are usually short term, they can lead to non-adherence. For full details of side effects and contraindications, see the summaries of product characteristics.

Memantine

Memantine (Ebixa, Lundbeck) is a voltage-dependent, moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction. It has a marketing authorisation for the 'treatment of patients with moderate to severe Alzheimer's disease'. It may be administered as monotherapy or as an adjunct to an AChE inhibitor. In 2005, the license was extended to include moderate disease. However, as the data for NICE technology appraisal guidance 111 were submitted in 2003–04, this license extension was not included.

The most common undesirable effects are dizziness, headache, constipation and somnolence. For full details of side effects and contraindications, see the summary of product characteristics.

3 The evidence

3.1 Clinical effectiveness

Evidence on clinical effectiveness was submitted by the Assessment Group and the manufacturers of donepezil, galantamine and memantine. For further details, please refer to the individual submissions and assessment report.

3.1.1 Background

NICE technology appraisal guidance 111 found evidence of benefit of AChE inhibitors mainly in terms of cognitive, functional and global outcomes, although the available evidence varied by agent, dose and significance.

The Assessment Group conducted a systematic review of the clinical evidence published since NICE technology appraisal guidance 111 was published in 2004. The effectiveness of the interventions (AChE inhibitors and memantine) was appraised in accordance with the marketing authorisations. For the population with mild Alzheimer's disease (defined as MMSE 21–26) the AChE inhibitors were compared with each other and best supportive care (that is, without treatment with any AChE inhibitors or memantine). For the population with moderate Alzheimer's disease (MMSE 10–20) the AChE inhibitors and memantine were compared with each other and with best supportive care. For the population with severe Alzheimer's disease (MMSE less than 10) memantine was compared with best supportive care. The Assessment Group identified 17 new randomised controlled trials and four systematic reviews of randomised controlled trials. These included 12 pairwise placebo-controlled comparisons (five of donepezil, three of galantamine, three of rivastigmine and one of memantine), four head-to-head studies of donepezil and rivastigmine, donepezil and galantamine and all three AChE inhibitors (two studies) and one study of memantine in combination with any of the AChE inhibitor.

If possible, new evidence was pooled with the evidence from 2004 using random effects meta-analysis compared with placebo. Different outcome measures were also pooled to explore the characteristics of the evidence base. Pooling of data from head-to-head trials was not possible because of the heterogeneity of the data. If data were sufficient, the Assessment Group pooled information on all technologies and their comparators in a mixed treatment comparison, using Bayesian Markov Chain Monte-Carlo sampling. The new, pooled and comparative evidence is summarised in section 3.1.2 by relevant outcome.

The Assessment Group considered the quality of the new placebo-controlled studies (published since 2004) to be 'disappointing'. Issues included the inappropriate use of last observation carried forward and observed cases analysis instead of intention-to-treat analysis, inadequate reporting of

randomisation and allocation, and the small size of studies for donepezil in particular. According to the Assessment Group, the quality of the new evidence provided by the head-to-head studies was limited by the poor quality of all but one of the studies. Important gaps in the evidence remain. The issues highlighted in the assessment report include lack of long-term data, and of evidence of the impact of the technologies on the quality of life of patients and carers, mortality and time to institutionalisation. The number and variation of outcome measures and their clinical relevance and sensitivity was also raised as an issue.

The manufacturer of donepezil also a conducted a systematic review of the evidence for donepezil in people with mild to moderate Alzheimer's disease published since 2004. It included new data from three randomised controlled trials, one subanalysis of a randomised controlled trial, two prospective longitudinal studies and three observational studies, six related subanalyses and four meta-analyses (two systematic reviews and two pooled analyses), in addition to data previously submitted.

The manufacturer of galantamine submitted information about new data published since 2004, open-label studies and data fromrandomised controlled trials already submitted for the NICE technology appraisal 111, in 2004 or during the appraisal process. Data were provided for six trials and four pooled analyses including mild, moderate and advance moderate subgroups.

The manufacturer of memantine submitted estimates of clinical effectiveness for the general moderate to severe population and a subgroup of patients with agitation, aggression or psychotic symptoms (APS). The manufacturer submitted a meta-analysis of six randomised controlled trials. The first three were in moderately severe to severe disease and the final three were in mild to moderate disease. Evidence from observational studies was also presented.

Submissions were also made by the Royal College of Psychiatrists, the British Geriatric Society and Alzheimer's Society, which made statements about and references to published clinical evidence.

3.1.2 Placebo controlled trials – evidence by outcome

The Assessment Group considered the outcomes for the four agents in relation to the population specified in their marketing authorisation (mild to moderate disease for AChE inhibitors and moderate to severe disease for memantine monotherapy). The Assessment Group presented a narrative summary of the clinical effectiveness evidence from NICE technology appraisal guidance 111, evidence from the new data and a pooled estimate that included the results of all of the studies. Because evidence from the new studies broadly confirmed the results of NICE technology appraisal guidance 111, only the pooled data of all studies are presented in this overview. A comparison is also made with the evidence submitted by the manufacturers. For full details of the new and previously submitted evidence, please refer to the individual manufacturer submissions.

The clinical effectiveness section uses the assessment report as the main source of evidence. The format of this section differs from that of the assessment report for presentational purposes including ease of reference and reading and no inferences should be made by indirect comparison of the technologies. The page reference of the assessment report is provided in the right-hand column of each table.

Cognition

NICE technology appraisal guidance 111 reported statistically significant benefits in cognition according to ADAS-cog for donepezil and galantamine and a dose-dependent benefit for rivastigmine compared with placebo. Similar trends were seen with MMSE scores but these were not always significant or measured. A statistically significant benefit was seen with the SIB for memantine but no significant benefit was shown using the MMSE versus placebo.

For donepezil, the Assessment Group found no new studies reporting the ADAS-cog at 12 or 24 weeks or MMSE at 12 weeks. The effectiveness estimates were therefore based on the studies included in NICE technology appraisal guidance 111. One new study was found that measured the effect of donepezil on cognition at 24 weeks follow-up. The overall pooled benefit for new and old data was significant on all scales and the standard mean difference of pooled outcomes increased with time for ADAS-cog. According to the manufacturer of donepezil, all 12 randomised controlled trials (from the NICE technology appraisal guidance 111 and current submissions that reported on cognition using the ADAS-cog, MMSE or SIB scales), showed a statistically significant difference favouring donepezil versus placebo with four of these reporting a statistically significant difference on two different cognitive scales.

Three new studies for galantamine were identified that measured cognition using ADAS-cog at 6 and 26 weeks and showed improvement. When the results of these were added to the results of NICE technology appraisal guidance 111, the pooled estimate demonstrated a statistically significant benefit of galantamine compared with placebo, which increased with time. According to the manufacturer of galantamine, established randomised controlled trial data from five placebo-controlled trials in mild to moderate Alzheimer's disease showed statistically significant benefit on ADAS-cog and this was reflected in the pooled data.

Three new studies for rivastigmine (patch and capsule were not differentiated) were identified that measured cognition using ADAS-cog and/or MMSE and showed significant benefit. When the results of these were added to the randomised controlled trials in NICE technology appraisal guidance 111, it demonstrated a statistically significant improvement in cognition with rivastigmine compared with placebo, although only for MMSE at 24–26 weeks.

One new randomised controlled trial of memantine monotherapy showed a statistically significant benefit measure using SIB with memantine compared with placebo. When data from this trial were added to those of NICE technology appraisal guidance 111, a statistically significant benefit was reported at 12 weeks, but this was not maintained at 24–48 weeks. Studies included in the manufacturer's meta-analysis for memantine reported a statistically significant benefit compared with placebo at the end of study or at 24 weeks for ADAS-cog or SIB. See table 2 for a summary of the pooled results for all technologies.

Table 2 New pooled data for cognitive outcomes (mean change from baseline versus placebo)

	MMSE	ADAS-cog	Combined cognitive/other	Page*
Mild to moderate Alzheimer's disease				
Donepezil	12 weeks (10 mg/day) = 1.165 (95% CI 0.884 to 1.445); p < 0.001 24 weeks (all dosages) = 1.206 (95% CI 0.839 to 1.573); p < 0.001	12 weeks (10 mg/day) = −1.969 (95% CI −3.379 to −0.559); p = 0.006 24 weeks (10 mg/day) = −2.895 (95% CI −3.608 to −2.182); p < 0.001	Cognitive outcomes SMD at 24–26 weeks (all dosages) = 0.395 (95% CI 0.293 to 0.497); p<0.001	86–8
Galantamine	Pooled data not available	12–16 weeks (maximum dose ≤ 24 mg/day) = −2.386 (95% CI −2.804 to −1.969); p < 0.001 21–26 weeks (maximum dose ≤ 24 mg/day) = −2.957 (95% CI −3.410 to −2.505); p < 0.001	Pooled data not available	109
Rivastigmine (capsule/ patch)	24–26 weeks (≥ 12 mg/d) = 1.022 (95% CI 0.634 to 1.409); p<0.001	24–26 weeks (≥ 12 mg/day) = −2.464 (95% CI −3.373 to −1.555); p < 0.001	Cognitive outcomes SMD at 24–26 weeks (all dosages) = 0.283 (95% CI 0.143 to 0.424); p < 0.001	132–4
Moderate to severe Alzheimer's disease				
Memantine	Pooled data not available	Pooled data not available	**SIB** at 12 weeks = 4.147 (95% CI 0.515 to 7.778); p = 0.025 **SIB** at 24–28 weeks = 3.254 (95% CI −2.233 to 8.741) p = 0.245	151

*Page of the assessment report

ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale. CI = confidence interval. MMSE = Mini Mental State Examination. SIB = Severe Impairment Battery. SMD = standard mean difference

Function

The guidance for NICE technology appraisal 111 generally showed significant benefit for galantamine in terms of function (including DAD and ADCS-ADL) but benefits were not always significant for donepezil or for some doses of

rivastigmine versus placebo. Memantine showed significant benefit on ADCS-ADL versus placebo.

One new poorly reported randomised controlled trial that measured functional outcomes for donepezil showed a statistically significant benefit from donepezil (5 mg/day) for activities of daily living in an observed cases measured population at 12 weeks follow-up. The heterogeneous collection of outcome measures prevented any quantitative synthesis of old and new evidence for individual measures since 2004. The pooled multiple outcome measure for functional outcome data from the studies in NICE technology appraisal guidance 111 showed a statistically significant benefit for donepezil at all doses compared with placebo at 24 weeks (no new data available). According to the manufacturer of donepezil, four randomised controlled trials showed a statistically significant difference favouring donepezil versus placebo on at least one scale and three reported non-significant trends in favour of donepezil. Additionally, the manufacturer cited a meta-analysis of seven randomised controlled trials of donepezil reporting a statistically significant benefit favouring donepezil versus placebo.

The Assessment Group found three new randomised controlled trials measuring functional outcomes for galantamine. The ADCS-ADL data from the new trials were pooled with those of the studies found in 2004, and the overall pooled estimates showed statistically significant functional benefit from galantamine compared with placebo at 21–26 weeks. The results of DAD were pooled at 21–26 weeks follow-up. They again showed a statistically significant benefit from galantamine compared with placebo. Two new studies were added to the meta-analysis of combined functional outcome measures at 21–26 weeks. The overall pooled estimate showed a statistically significant functional benefit from galantamine compared with placebo. The manufacturer referred to four established placebo-controlled randomised controlled trials that showed benefit in terms of ADCS-ADL or DAD, of which some were statistically significant benefits, including the pooled data.

Two of the three new studies found since 2004 reported statistically significant functional benefit from rivastigmine compared with placebo. These used PDS and ADCL-ADL as outcome measures. The overall pooled estimate for PDS at 24–26 weeks showed a statistically significant benefit of rivastigmine. Two new studies were found to add to this combined meta-analysis of functional outcomes at 24–26 weeks. The overall pooled estimate showed a statistically significant benefit from rivastigmine compared with placebo.

The results from the new study showed no significant benefit on functional outcome measured by ADCS-ADL for memantine monotherapy compared with placebo at 12 weeks, but a statistically significant benefit was seen when measured with the Functional Assessment Staging (FAST) instrument. The data were synthesised with the existing evidence in random-effects meta-analysis. Two studies provided data for functional effect as measured by ADCS ADL19 version. The results were not statistically significant at 12 weeks and were barely significant at 24–28 weeks. The overall pooled estimate showed a statistically significant benefit of memantine compared with placebo. The manufacturer's meta-analysis for memantine in moderate to severe disease showed a statistically significant difference compared with placebo on the ADCS-ADL19 or ADCS-ADL23. See table 3 for a summary of pooled results for all technologies.

Table 3 New pooled data for functional outcomes (mean change from baseline versus placebo)

	ADCS–ADL	DAD	Combined functional	Page*
Mild to moderate Alzheimer's disease				
Donepezil	Pooled data not available	Pooled data not available	Functional outcomes (SMD) at 24 weeks (all dosages) = 0.298 (95% CI 0.144 to 0.452); p < 0.001	89
Galantamine	12–13 weeks (≤ 24 mg/day) = 1.394 (95% CI 0.590 to 2.198); p < 0.001 21–26 weeks (≤ 24mg/day) = 2.234 (95% CI 1.328 to 3.140); p < 0.001	21–26 weeks (≤ 24mg/day) = 3.761 (95% CI 1.661 to 5.861); p < 0.001	Functional outcomes (SMD) at 21–26 weeks (all dosages) = 0.265 (95% CI 0.182, 0.348); p < 0.001	112–3
Rivastigmine (capsule/ patch)	Pooled data not available	Pooled data not available	Functional outcomes (SMD) at 24–26 weeks (all dosages) = 0.205 (95% CI 0.118 to 0.292); p < 0.001 Also PDS at 24–26 weeks (12 mg/d) = 3.103 (955 CI 1.805 to 4.402); p<0.001	135–6
Moderate to severe Alzheimer's disease				
Memantine	ADCS–ADL19 at 12 weeks = 0.877 (95% CI −0.089 to 1.842); p = 0.075 ADCS–ADL19 at 24–28 weeks = 1.408 (955 CI = 0.036, 2.780); p = 0.044	Pooled data not available	FAST at 24–28wk = −0.341 (95% CI −0.554 to −0.127); p = 0.002	152–3

*Page of the assessment report

ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living. CI = Confidence interval. FAST = Functional Assessment Staging. MMSE = Mini Mental State Examination. PDS = Progressive Deterioration Scale. SIB = Severe Impairment Battery. SMD = standard mean difference

Behaviour

NICE technology appraisal guidance 111 concluded that the evidence generally did not show statistically significant benefit in terms of behavioural outcomes (mainly NPI) with any of the AChE inhibitor treatments. Some beneficial effect was seen with donepezil and some dose-dependent benefit

was statistically significant with galantamine, but generally results varied. Memantine showed a statistically significant benefit in combination therapy but not monotherapy.

None of the newly identified studies for donepezil provided additional data for behavioural function, so the results were based on studies included in NICE technology appraisal guidance 111, which noted no statistically significant benefit from donepezil compared with placebo at 12 or 24 weeks measured with NPI. According to the manufacturer of donepezil, three randomised studies found a statistically significant difference between donepezil and placebo on NPI score, with a fourth study finding a statistically significant difference for agitation or aggression but not total score. The manufacturer also refers to six pooled studies that showed a statistically significant difference in favour of donepezil on NPI total score compared with placebo.

Only one included study provided additional data for the effectiveness of galantamine in relieving behavioural symptoms, when compared with placebo. However, this did not show any statistically significant benefit. Only one new study added evidence to this meta-analysis. At 13 weeks no significant benefit was found but at 21–26 weeks the overall pooled estimate favoured galantamine significantly. The manufacturer of galantamine, referred to one study that showed statistically significant benefits in terms of NPI score and another two placebo-controlled trials that showed a benefit in terms of NPI score that did not achieve significance. Mixed results were reflected in the pooled data.

For rivastigmine, two new studies were found that measured behavioural outcomes. One small study found a statistically significant benefit from rivastigmine. The other, much larger study, did not. The data identified by this review and NICE technology appraisal guidance 111 are sparse and too heterogeneous to permit meaningful quantitative synthesis.

The study for memantine monotherapy that was published after 2004 measured behavioural outcomes using NPI and the Behavioural Rating Scale

for Geriatric Patients (BGP). Neither measure showed a statistically significant benefit of memantine. The data were pooled with the existing data at 24−28 weeks, which did not show a statistically significant gain from memantine compared with placebo. The results of the meta-analysis by the manufacturer of memantine in moderate to severe disease showed a statistically significant (p = 0.03) benefit in terms of NPI and NPI-Nursing Home version. See table 4 for a summary of all results.

Table 4 New pooled data for behavioural outcomes (mean change from baseline versus placebo)

	NPI	Page*
Mild to moderate Alzheimer's disease		
Donepezil	12 weeks (all dosages are 10 mg/day) = −2.249 (95% CI −5.105 to 0.606); p = 0.123 24 weeks (all dosages are 10 mg/day) =−3.116 (95% CI −8.165 to 1.932); p = 0.226	91
Galantamine	13 weeks (all dosages) = −0.746 (95% CI −1.835 to 0.342); p=0.179 21–26 weeks (all dosages) = −1.455 (95% CI −2.585 to −0.324); p=0.012	115
Rivastigmine (capsule /patch)	Pooled data not available	n/a
Moderate to severe Alzheimer's disease		
Memantine	24–28 weeks = −1.608 (055 CI −4.739 to 1.523); p = 0.314	154
*Page of the assessment report CI = Confidence interval. NPI = neuropsychiatric inventory. SMD = standard mean difference.		

Global function

NICE technology appraisal guidance 111 concluded that there was a statistically significant benefit of in terms of global outcomes with donepezil and rivastigmine using the CIBIC-plus, although this varied according to the dose of rivastigmine. A higher proportion of patients improved on galantamine but the pooled outcome was not significant. Memantine showed some benefit in terms of the CIBIC-plus.

One of the new studies measured global outcomes for donepezil and reported a statistically significant benefit on the clinical dementia rating (CDR). All of

the evidence on the CIBIC-plus was based on NICE technology appraisal guidance 111. A meta-analysis of the effectiveness of donepezil for the CIBIC-plus reported a statistically significant benefit of donepezil 10 mg/day compared with placebo at 12 and 24 weeks. The Assessment Group did not find any new studies that measured global outcomes at 24-26 weeks. The pooled multiple outcome measures for the global outcome data from the studies in NICE technology appraisal guidance 111 showed a statistically significant benefit for donepezil at all doses compared with placebo at 24–26 weeks. According to the manufacturer of donepezil, global function (CIBIC-Plus, CDR-SB or GBS) was measured in nine of the studies presented in new and previous submissions with statistically significant results in favour of donepezil in seven of them. A submitted meta-analysis of ten trials also showed significant improvement in global function compared with placebo.

Two new studies were found that measured global outcomes for galantamine. One found a significant benefit from galantamine measured by the CIBIC-plus compared with placebo at 13−16 weeks. When the new studies' data were pooled with existing evidence the overall pooled estimates of the CIBIC-plus at 26 weeks showed a statistically significant benefit from galantamine compared with placebo. According to the manufacturer of galantamine, established randomised controlled trial data show that in four out of five placebo-controlled trials in people with mild to moderate Alzheimer's disease, statistically significant benefits of galantamine were seen with CIBIC-plus. This was statistically significant benefit was reflected in the pooled data.

For rivastigmine, the two new studies in this comparison that reported global outcomes had conflicting results. There were mostly significantly favourable results with the CIBIC-plus but not the GDS. Data from the new studies were pooled with the existing evidence in random-effects meta-analyses using the CIBIC-plus at 26 weeks and the GDS at 26 weeks. The meta-analysis showed a statistically significant benefit from rivastigmine at 26 weeks. The GDS meta-analysis also showed a statistically significant benefit from rivastigmine

at 26 weeks. The pooled results from both outcomes showed an overall statistically significant benefit for rivastigmine compared with placebo.

One new study for memantine monotherapy measured global outcomes with the CIBIC-plus but the differences found were not statistically significant. When new data were pooled with the existing studies, the overall pooled estimate showed a statistically significant beneficial effect from memantine compared with placebo. Studies included in the meta-analysis for memantine included CIBIC-Plus or ADCS-CGI-C. The standard mean difference in the meta-analysis for memantine in moderate to severe disease for global outcomes compared with placebo was statistically significant. See table 5 for a summary of the pooled results for all technologies.

Table 5 New pooled data for global outcomes (mean change from baseline versus placebo, 95% CI)

	CIBIC-plus	Other	Other	Page*
Mild to moderate Alzheimer's disease				
Donepezil	12 weeks (10 mg/day) = −0.377 (95% CI −0.490 to −0.264); p < 0.001 24 weeks (10 mg/day) = −0.429 (95% CI −0.549 to −0.309); p < 0.001	Clinical dementia rating at 12 weeks (all dosages) −0.263 (95% CI −0.435, −0.091); p = 0.003 24 weeks (all dosages) = −0.568 (95% CI −0.849 to −0.288); p < 0.001	Global outcomes (SMD) at 24–26 weeks (all dosages) = 0.377 (95% 0.270 to 0.484); p < 0.001	93–4
Galantamine	26 weeks – (maximum dose ≤ 24 mg/day) = −0.196 (95% CI −0.299 to −0.093); p < 0.001	Pooled data not available	Pooled data not available	117
Rivastigmine (capsule /patch)	26 weeks (12 mg/day) = −0.420 (95% CI −0.553 to −0.288); p < 0.001	GDS at 26 weeks (12 mg/day) = 0.196 (95% CI 0.119 to 0.274); p < 0.001	Global outcomes (SMD) at 24–26 weeks (all dosages) = 0.231 (95% CI 0.155 to 0.307); p < 0.001	139–40
Moderate to severe Alzheimer's disease				
Memantine	24–28 weeks −0.300 (955 CI −0.471 to −0.129) p < 0.001	Pooled data not available	Pooled data not available	155

*Page of the assessment report.

CIBIC = Clinician's Interview-based Impression of Change. GDS = Global Deterioration Scale. SMD = standard mean difference.

Quality of life and other outcomes

The Assessment Group noted that none of the new randomised studies included in the assessment report provided any additional data on quality of life with donepezil, galantamine, rivastigmine or memantine compared with placebo, and no such data were identified in NICE technology appraisal

guidance 111. Additionally, the randomised controlled trials included in the assessment report showed no new evidence for mortality, institutionalisation or data beyond 28 weeks.

Adverse effects

According to the Assessment Group, none of the five newly identified studies for donepezil provided data on adverse events observed under randomised conditions except for limited data from one study (pages 167-170 of the assessment report). Overall for galantamine in two new studies, there was a high percentage of any adverse event in both studies in treatment and control groups (any adverse events: treatment 79–84%, placebo = 62–70%). For rivastigmine, overall there were a high percentage of any adverse events, ranging from 51% to 91% in the treatment groups, and 46% to 76% in control groups. The main adverse events were gastrointestinal. The lower dose (9.5 mg/day) transdermal patch produced fewer side effects than the capsule (12 mg/day). The proportion of any adverse events for memantine in the new study was similar in treatment and control groups (treatment = 74%, control = 73%). The main adverse events in the memantine group were agitation and hypertension, and agitation and falls in the control group.

The manufacturers also presented safety data (see individual submissions for details). In summary, the manufacturer of donepezil referred to the new data since 2004 and stated that new data was consistent with that previously submitted. The manufacturer of galantamine did not present any new data. The manufacturer of memantine refers to safety reports since 2002, two safety reviews and a meta-analysis and concluded that memantine was well tolerated when used as monotherapy or as an adjunct therapy.

Correlation of outcomes

The Assessment Group conducted meta-regression analysis to explore the statistical heterogeneity across studies, looking at population age, population sex and baseline MMSE score (as a proxy for disease severity). Only one graph showed a significant relationship between baseline MMSE score and functional outcomes at 24 weeks for all doses of donepezil. However,

because of the small number of studies in each analysis and the fact that the data were assessed at a population level (which may not reflect the individual level) the Assessment Group felt that these results may be ambiguous.

3.1.3 Summary of new evidence from placebo-controlled trials

Although more evidence has become available since 2004 the Assessment Group concluded that the impact on previous conclusions about effectiveness appeared small. For the AChE inhibitors, the new studies supported and strengthened the previous evidence of benefit in terms of cognitive outcomes, but results for other outcomes were mixed with no significant benefit found in terms of behaviour. A new transdermal patch for rivastigmine was as effective and had fewer side effects than the capsule. For memantine monotherapy, the new evidence did not support evidence of benefit compared with placebo for any outcome. For further information on the summary of the clinical evidence please refer to section 4.10 on pages 190–191 of the assessment report. Table 6 summarises the changes in the evidence.

Table 6 Visual summary by Assessment Group of changes to the estimates of clinical effectiveness evidence since 2004

Outcome	Data type	Donepezil	Galantamine	Rivastigmine	Memantine
Cognitive	New	~ (5)	✓ (3)	✓ (3)	✕ (1)
	Existing	~ (6)	✓ (6)	~ (3)	~ (1)
	Pooled	✓	✓	✓	~[1]
Functional	New	✓ (1)	~ (3)	✓ (3)	✕(1)
	Existing	~ (8)	✓ (3)	~ (2)	✓ (1)
	Pooled	✓	✓	✓	~[2]
Behavioural	New	–	✕ (1)	✕ (2)	✕ (1)
	Existing	~ (4)	~ (2)	✕ (2)	✕ (1)
	Pooled	✕[3]	~[4]	–	✕
Global	New	✓ (1)	~ (2)	✓ (2)	✕ (1)
	Existing	~ (7)	✓ (5)	✓ (3)	✓ (1)
	Pooled	✓	✓	✓	✓
Change in direction of evidence	All	↑	↓	↑	↔
Change in amount of evidence	All	↑	↑	↑	↑
Increased precision	All	↑	↑	↑	↔[5]

Source: table 73, page 191 of the assessment report.

~ The results of studies in this group were mixed for this outcome, some showing significant gain, others not. ✓ The results of studies in this group all showed statistically significant benefit ($p < 0.05$) for this outcome. ✕ The results of studies in this group did not show statistically significant benefit ($p < 0.05$) for this outcome. – This outcome was not measured for this drug. ↑ Positive change in direction. ↔ No change in direction.

Numbers in brackets show the number of studies.

[1] The pooled results were significant at 12 weeks but not at 24-28 weeks follow-up.

[2] The pooled results were significant at 24–28 weeks with the FAST and the ADCS-ADL but not at 12 weeks with the ADCS-ADL.

[3] The pooled results were of existing studies.

[4] The pooled results were significant at 21–26 weeks but not at 13 weeks follow-up.

[5] The quality of the new evidence was not as good as the previous evidence.

3.1.4 Head-to-head comparisons of the AChE inhibitors (section 4.7.1.1, pages 156–166 of the assessment report)

The Assessment Group identified four head-to-head randomised controlled trials (two comparing all three AChE inhibitors, one comparing donepezil with rivastigmine and one comparing donepezil and galantamine) but only one of the studies was of sufficiently high quality to inform this review. The other studies were considered of poor quality and showed mixed results. The included study noted that over 2 years there was no statistically significant difference between rivastigmine and donepezil for cognitive outcomes (MMSE and SIB). Patients taking rivastigmine did significantly better than those taking donepezil in the primary analysis of functional outcomes (p =0.047–0.007). No significant difference was seen between donepezil and rivastigmine for behavioural outcomes (NPI). The head-to-head study showed that patients taking rivastigmine did significantly better than those taking donepezil in terms of global outcomes (GDS). None of the newly identified, head-to-head, randomised studies investigated quality of life with the technologies under assessment, and no such data were identified in NICE technology appraisal guidance 111. The most common adverse effects were nausea, diarrhoea, vomiting and headache.

3.1.5 Mixed treatment comparison

If data were sufficient, the Assessment Group pooled information on all technologies and their comparators simultaneously in a mixed treatment comparison, using Bayesian Markov Chain Monte-Carlo sampling. This approach was not taken by the manufacturers as it was considered inappropriate due to differences in the trial populations.

Table 7 notes the probability of each technology being the most clinically effective treatment for Alzheimer's disease. For example, donepezil has a 0.0475 probability of being the most clinically effective treatment for cognitive symptoms at 12–16 weeks compared with galantamine and rivastigmine, which have a 0.421 and 0.0104 probability of being the most clinically effective, respectively.

Table 7. Results of the Assessment Group mixed treatment comparison

Technology	Comparison with placebo			Probability it is most effective
	Effect	95%CI	Probability it is more effective than placebo	
ADAS-cog at 12–16 weeks (mean change from baseline; all measurement populations)				
Placebo	–	–	–	0.000
Donepezil	−2.209	−2.951 to –1.452	1.000	0.475
Galantamine	−2.176	–2.725 to −1.540	1.000	0.421
Rivastigmine	−1.700	−2.728 to −0.751	0.999	0.104
Memantine	–	–		–
ADAS-cog at 21–26 weeks (mean change from baseline; all measurement populations)				
Placebo	–	–	–	0.000
Donepezil	−2.431	−3.174 to −1.709	1.000	0.107
Galantamine	−2.986	−3.591 to −2.405	1.000	0.885
Rivastigmine	−1.978	−2.630 to −1.303	1.000	0.009
Memantine	–	–	–	–
MMSE at 12–13 weeks (mean change from baseline; all measurement populations)				
Placebo	–	–	–	0.000
Donepezil	1.145	0.677 to 1.637	1.000	0.537
Galantamine	0.259	−1.214 to 1.761	0.646	0.075
Rivastigmine	1.057	0.283 to 1.852	0.993	0.389
Memantine	–	–	–	–
MMSE at 24–26 weeks (mean change from baseline; all measurement populations)				
Placebo	–	–	–	0.000
Donepezil	1.235	0.747 to 1.778	1.000	0.670
Galantamine	–	–	–	–
Rivastigmine	1.073	0.358 to 1.809	0.993	0.330
Memantine	–	–	–	–
ADCS-ADL at 12–16 weeks (mean change from baseline; all measurement populations)				
Placebo	–	–	–	0.008
Donepezil	–	–	–	–
Galantamine	1.410	−0.316 to 3.148	0.956	0.494
Rivastigmine	1.410	−1.033 to 3.842	0.907	0.498
Memantine	–	–	–	–
ADCS-ADL at 21–26 weeks (mean change from baseline; all measurement populations)				
Placebo	–	–	–	0.001
Donepezil	–	–	–	–
Galantamine	2.238	0.528 to 3.943	0.990	0.547
Rivastigmine	2.091	−0.322 to 4.519	0.962	0.451
Memantine	–	–	–	–
NPI at 12–13 weeks (mean change from baseline; all measurement populations)				
Placebo	–	–	–	0.006
Donepezil	−1.960	−4.095 to 0.033	0.973	0.799
Galantamine	−0.788	−2.872 to 1.267	0.810	0.195
Rivastigmine	–	–	–	–
Memantine	–	–	–	–
NPI at 21–28 weeks (mean change from baseline; all measurement populations [all are classical ITT or LOCF analysis])				
Placebo	–	–	–	0.000
Donepezil	−2.683	−5.673 to 0.207	0.966	0.576
Galantamine	−1.462	−3.438 to 0.526	0.940	0.129
Rivastigmine	−0.366	−3.308 to 2.554	0.612	0.052
Memantine	−1.600	−4.762 to 1.540	0.845	0.243

CIBIC-plus at 12–16 weeks (all measurement populations)				
Placebo	–	–	–	0.001
Donepezil	−0.338	−0.647 to −0.079	0.985	0.373
Galantamine	−0.370	−0.746 to –0.025	0.978	0.541
Rivastigmine	–0.007	–0.492 to 0.477	0.520	0.027
Memantine	−0.071	−0.591 to 0.448	0.647	0.058
CIBIC-plus at 24–28 weeks (all measurement populations)				
Placebo	–	–	–	0.000
Donepezil	−0.392	−0.549 to −0.251	1.000	0.546
Galantamine	−0.222	−0.356 to −0.091	0.997	0.010
Rivastigmine	−0.354	−0.508 to −0.203	1.000	0.285
Memantine	−0.300	−0.507 to −0.100	0.996	0.159
GDS at 24–28 weeks (mean change from baseline; all measurement populations)				
Placebo	–	–	–	0.012
Donepezil	0.161	−0.402 to 0.720	0.866	0.453
Galantamine	–	–	–	–
Rivastigmine	0.171	−0.159 to 0.486	0.941	0.491
Memantine	−0.099	−0.662 to 0.450	0.189	0.043
Source: tables 52–72, pages 183–189 of the assessment report				

Combination therapy

The Assessment Group assessed the clinical effectiveness of memantine combination therapy separately from monotherapy. This was different from the approach taken in NICE technology appraisal guidance 111 and by the manufacturer of memantine. The group found one new trial that compared memantine plus a stable dose AChE inhibitor with an AChE inhibitor and placebo. This trial did not show any benefit from combining memantine with an AChE inhibitor on cognitive, functional, behavioural or global outcomes. A trial that compared memantine plus donepezil with donepezil and placebo was included in NICE technology appraisal guidance 111. Pooling the new trial with the previous trial of memantine in combination with an AChE inhibitor did not show any additional benefit from combination therapy.

Discussion points and further information on clinical effectiveness

According to the Assessment Group, despite an increase in the amount and precision of available evidence for the clinical effectiveness of AChE inhibitors and memantine, the impact on previous conclusions is relatively small. The assessment report highlighted inconsistencies in the results of available studies, issues in terms of the quality of available evidence and the gaps left

by the evidence in terms of high quality long-term data, quality–of-life data, impact on carers, time to institutionalisation and mortality.

The Assessment Group cite several systematic reviews that were published since 2004. However, it is difficult to compare results with those of the Assessment Group due to differences in the methodologies. A Cochrane review concluded that high doses of rivastigmine offered statistically significant benefits in patients with mild to moderate Alzheimer's disease versus placebo. Another, including a meta-analysis, concluded that AChE inhibitors provided benefits in terms of cognitive function and activities of daily living, and galantamine improved psychological symptoms in mild to moderate dementia. Another concluded that for AChE inhibitors and memantine there was a small effect size in mild to moderate Alzheimer's disease. For further details, see pages 72 to 75 of the assessment report.

The Assessment Group concluded that the evidence in the manufacturer's submissions was broadly consistent with its own although it highlighted that there were differences between the studies included by the manufacturers and their own review. Appendix 10 of the assessment report describes the reasons why some studies were included by the manufacturers were excluded by the Assessment Group, although the Assessment Group was not able to make a complete comparison of methodologies with the information available. The MAG-D study of memantine in the treatment of agitation was ongoing at the time of the submission and therefore not included in any submission.

The manufacturer of donepezil included prospective longitudinal and observational studies to support the view that cognitive benefits from donepezil are maintained for up to 3 years (pages 60–61 of the manufacturer's submission). In addition, the manufacturer presented evidence from randomised and non-randomised controlled trials to demonstrate that benefit was lost on cessation of treatment, the benefits of continuing treatment despite initial decline or stabilisation of MMSE and the impact of improvement of neuropsychiatric symptoms on caregiver stress and

burden (pages 69-70 of the manufacturer's submission). The manufacturer of memantine also included non-randomised clinical-effectiveness data for memantine that was not included by the Assessment Group because of lack of randomisation (page 27 of the manufacturer's submission). The manufacturer also conducted a subgroup analysis of patients with APS (pages 22-26 of the manufacturer's submission) and stated that memantine is associated with enhanced treatment benefits (control of symptoms after 12 weeks and greater treatment effects on cognition and functioning in this population) in this subgroup.

Alzheimer's Society submitted evidence from a survey in 2004 of people with dementia or their carers (the vast majority of responses) that reported the top five spontaneously mentioned benefits of AChE inhibitors to be (as reported): stabilising and slowing the illness; being happier, brighter, more aware and more active; improved and helped memory loss; being calmer and less aggressive; and being more independent and taking care of personal needs. The survey mentioned that ensuring adherence was an issue for some carers.

3.2 Cost effectiveness

3.2.1 Systematic review of economic evaluations

The Assessment Group conducted a systematic review of new literature available since the publication of NICE technology appraisal guidance 111 in 2004. The Assessment Group identified 23 studies of cost effectiveness published since 2004, which included eight specifically for donepezil, one for rivastigmine, two for galantamine, six for memantine and one that reported on the cost effectiveness of both donepezil and rivastigmine. Some of these economic evaluations were conducted alongside clinical trials and are summarised in tables 74–77 in the assessment report.

According to the Assessment Group, these publications generally support the cost effectiveness of the AChE inhibitors and memantine in the treatment of the all stages of Alzheimer's disease (page 197-209 of the assessment report). Most of the publications applied the existing model of Alzheimer's

disease (NICE technology appraisal guidance 111) to new settings and one in particular provided by the manufacturer of donepezil attempted to overcome problems observed with the previous model from NICE technology appraisal guidance 111 using a discrete event simulation model (see section 3.2.3 of this document).

3.2.2 Submissions from manufacturers

The manufacturer of donepezil (Eisai/Pfizer) and the manufacturer of memantine (Lundbeck) each submitted an economic model. No new economic models were submitted by the manufacturers of galantamine and rivastigmine. The manufacturer of galantamine (Shire) highlighted issues with the previous model from NICE technology appraisal guidance 111 (see 3.2.4).

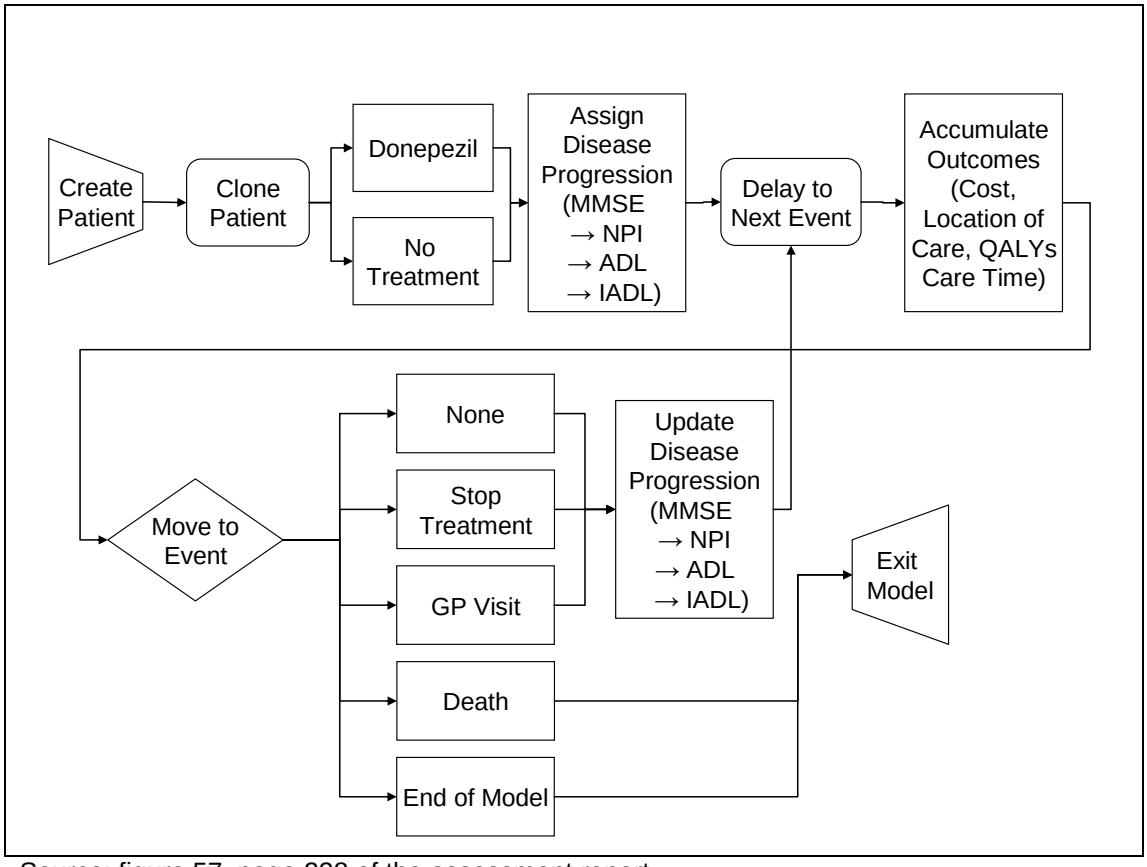
3.2.3 Economic model by the manufacturer of donepezil

The manufacturer submitted an economic evaluation that compared the cost effectiveness of donepezil with best supportive care in people with mild to moderate Alzheimer's disease. Separate subgroup analyses were also presented for subpopulations with mild and moderate disease.

The model was based on a discrete event simulation approach over a lifetime (25 year) time horizon. The baseline characteristics (including age, sex, race, measures of cognition, function and behaviour [MMSE, ADL, IADL and NPI] and concomitant treatments) of the model population were based on a randomised controlled trial of 826 patients of whom 221 had mild disease and the remainder had moderate disease. The manufacturer built a multifactorial model of the disease and included individual patient variation and longer-term data (from a 52-week open-label study). The model used a weighted sampling approach to sample 1000 individuals from a trial population, and patients were then cloned and allocated to donepezil or best supportive care (and no AChE inhibitor treatment) arms. The manufacturer noted that unlike Markov models, which have pre-defined health states and fixed time periods, this discrete event simulation was based on variable time between a number of possible events (such as stopping treatment, GP visits, and death) after which the

model updates the costs and QALYs for individual patients. The model also updates patient characteristics every 3 months. Cost and benefits were discounted at 3.5%.

Figure 1 Simplified representation of the donepezil Alzheimer's disease model taken directly from the manufacturer's submission



Source: figure 57, page 228 of the assessment report

Disease progression was measured using cognition, activities of daily living and behaviour (MMSE, ADL, IADL NPI). The annual change in MMSE regression was based on data from 721 patients from a US registry (the CERAD study) with unknown severity of Alzheimer's disease who had never received treatment for Alzheimer's disease. The updated MMSE score was then used to predict the change in ADL, IADL and NPI. The effectiveness of donepezil was included using regression equations of these four measures of disease progression, which were derived from a meta-analysis of eight randomised controlled trials that assumed the same treatment effect for both mild and moderate Alzheimer's disease. The proportion of people

institutionalised depended on severity (see table 82 of the assessment report) and a consultation visit took place every 6 months during treatment. Discontinuation data were taken from 88 patients. Patient utilities were based on a Swedish study using the EQ-5D and carer proxy responses. Carer utilities were estimated using SF-36 scores and the Brazier algorithm from three clinical trials. Carer utility accounted for approximately 10% of the total QALYs but did not include the impact on carer utility of patients entering an institution. NHS and personal social services (PPS) costs were included along with costs to the individual and their family. NHS reference costs, list drug prices and a report by Dementia UK (2007) were used for cost estimates, which were inflated to current prices (see table 11 on page 94 of the manufacturer's submission).

The manufacturer's base-case results estimated that donepezil dominated best supportive care because it was less costly and more effective in people with mild, moderate and mild to moderate Alzheimer's disease (MMSE ≥ 10 and ≤ 26 respectively). The manufacturer reported per patient QALY gains of 0.133 and 0.098 and estimated total per patient cost savings of £3379 and £1889 for groups with mild and moderate disease, respectively. When the overall mild to moderate disease population was considered, total cost savings amounted to £2354 and people gained an average of 0.109 QALYs including patient utility alone and 0.121 including patient and carer utilities. For further information refer to tables 12–14 on pages 96–97 of the manufacturer's submission.

All but one of the one-way sensitivity analyses conducted by the manufacturer of donepezil in the mild and moderate disease populations (including varying the time horizon, discount rate, MMSE progression, treatment effect, discontinuation, treatment duration, costs of care, costs of nursing home care, patient and carer QALY effect, cost of physician visit, and the 30–50% reduced price of donepezil after loss of patent protection in 2012) resulted in donepezil being dominant. The exception was when nursing home costs were reduced by 50%, which changed the incremental difference in costs from a

cost saving of £3379 in the base case to an increased cost of £275, which gave an ICER of £1866 per QALY gained for mild Alzheimer's disease. When nursing costs were reduced in the moderate disease population, the costs were increased from a cost saving of £1889 in the base case to an increase of £1370 giving an ICER of £7093 per QALY gained. The probabilistic sensitivity analysis reported a 78% and 74% probability of being cost effective at a threshold of £30,000 (74% and 70% at a threshold of £20,000) per QALY gained in the mild and moderate disease populations respectively.

Issues raised by the Assessment Group (assisted by the Decision Support Unit because of its additional expertise in discrete event simulation modelling) included (section 6.3.4.1, pages 233–245 of the assessment report):

- unclear generalisability of the CERAD (US-based) study
- double counting of MMSE in the regression equations for NPI, ADL and IADL
- the data for the probability of requiring institutionalised care are based on a nursing home population
- uncertainty about the quality of inputs including the link that was made between MMSE and institutionalisation and overestimation of treatment effect
- the model does not take into account that carer utility may increase with institutionalisation
- inclusion of non-NHS/PSS costs not in line with reference case
- the fact that it was not a pure discrete event simulation approach because the cost and utility inputs were based on a cohort approach
- uncertainties about the probabilistic sensitivity analysis

The Assessment Group made several changes to the manufacturer's model, which included corrected MMSE scaling, hazard calculations and life expectancy. These amendments had little impact on the manufacturers deterministic and probabilistic ICER, which continued to show that donepezil dominated best supportive care in mild and moderate Alzheimer's disease.

The manufacturer of donepezil included evidence that patients showing clinical worsening may benefit from treatment compared with those on placebo or who are untreated (page 40 of the manufacturer's submission). The manufacturer also included a responder analysis that showed how results varied depending on the definition of response (pages 40–41 of the manufacturer's submission). The manufacturer also used these data to demonstrate the effects of treatment on the carer.

3.2.4 Submission by the manufacturer of galantamine

The submission by the manufacturer of galantamine did not include an economic model but highlighted issues arising from the Southampton Health Technology Assessment Centre (SHTAC) model on which NICE technology appraisal guidance 111 was based. The manufacturer reported that, if particular issues were addressed, the ICERs for galantamine would be lower and tend towards cost effectiveness for mild patients. The issues to be addressed (detailed on pages 5-6 of the submission) included:

- the need to include long-term efficacy data
- recognition of the full impact of decline in untreated mild patients
- overestimation of mortality
- then need for current cost data
- recognition of 'no change' on global efficacy after 6 months or longer
- consideration of costs to the individual, carer time and costs
- exploration of responder analyses

3.2.5 Economic model by the manufacturer of memantine

The manufacturer submitted a Markov cohort model of the cost effectiveness of memantine compared with best supportive care over a 5-year time horizon in two targeted populations: people with moderate to severe Alzheimer's disease and a subgroup of people with APS at baseline based on the NPI scale (≥ 3). The model was similar to the SHTAC-AHEAD model used in NICE technology appraisal guidance 111 with three states: pre-full-time care; full-time care; and death. The definition of full-time care in the manufacturer's

submission was to be either dependent or institutionalised. SHTAC defined full-time care as equivalent institionalised care including day and night supervision of personal care, safety and medical care. Transition probabilities, including the baseline probability (on no treatment) of moving from pre-full-time care to full-time care and the probability of death were estimated using data from the London and South-East Region (LASER-AD) UK epidemiological study in which 45% of patients in the study had APS. Predictors of the length of time to patients entering full-time care included measures of cognition (ADAS-Cog), function (ADCS-ADL), behaviour (NPI) and time in months. The clinical effectiveness of memantine, for which no additional benefit was assumed beyond 6 months, was based on a meta-analysis of six clinical trials. Weighted mean differences were applied to the risk equation estimating monthly probability of entering full-time care to incorporate treatment effect. NHS and PSS costs were included. Resource use data were taken from the LASER study and the Personal Social Services Research Unit (PSSRU), and MIMS March 2010 was used for costs, which were discounted at 3.5%. Indirect costs and quality-of-life effects on relatives and carers were not included. Utility estimates were derived from the LASER-AD study, which involved mapping of three instruments (HSQ-12, Ferm's D test and QoL-AD) onto the EQ-5D. The manufacturer ran the model probabilistically.

The manufacturer found that memantine dominated no pharmacological treatment because additional QALYs were gained (0.031) at no additional cost (a cost saving of £1711). Memantine treatment was associated with a delay to full-time care of 6 weeks. Additional treatment benefits were reported in the subgroup of patients with APS in whom the delay to full-time care was prolonged by up to 11 weeks with incremental QALY gains of 0.069 and a cost saving of £4971 (see page 37 of the manufacturer's submission).

Sensitivity analyses to explore differences in the treatment effect, discount rate, cost pre-full-time care, costs of full-time care and using alternative sets of utilities on cost effectiveness all continued to show memantine dominated best

supportive care for the overall population and subgroups (page 39 and 41 of the manufacturer's submission).

The Assessment Group highlighted several issues with the memantine model. The subgroup that was analysed was not previously accepted by the Appraisal Committee. The manufacturer did not include an AChE inhibitor as a comparator for the moderate disease population as specified in the scope. There was uncertainty about the risk equation because of lack of clarity over generalisability of the LASER-AD study, lack of clarity about the categorisation of 'dependence', inclusion of data from patients with mild disease, poor reporting of statistical analyses and lack of validation from an external source. There were concerns about the measure of treatment effect because trials inappropriately used observed cases and last observation carried forward analysis instead of intention-to-treat, which may have biased clinical effectiveness estimates. There was also uncertainty about the methods used to map one outcome measure to another (mapping one health-related quality-of-life measure onto another, mapping SIB onto the ADAS-cog and rescaling one version of ADCS-ADL to another), pooling data for combination therapy and monotherapy, and the use of NPI rather than NPI hallucinations as a predictor. There was also a lack of clarity over sources of data, inclusion of costs borne by individuals and retrospective collection of resource data in LASER-AD study. Benefits to carers were not included in the model and mapping of health-related quality-of-life data to EQ-5D was poorly described. The Assessment Group raised the question whether 90% probability of cost effectiveness as reported in the manufacturer's submission was plausible given the lack of evidence on the clinical benefit of memantine.

The manufacturer of memantine included an analysis of a subgroup of patients with moderate to severe Alzheimer's disease with APS to show that memantine offers enhanced benefits in this subgroup in terms of cognition and function (pages 22–23 of the manufacturer's submission). The manufacturer also included an indirect comparison with risperidone (page 26 of the manufacturer's submission), which was not a comparator in the scope

and therefore outside the scope of this review. The MAG-D study was ongoing at the time of writing the assessment report, so was not included by the Assessment Group.

3.2.6 Assessment Group economic model

The Assessment Group reviewed various options for the modelling approach. This process is described on pages 257 to 263 of the assessment report.

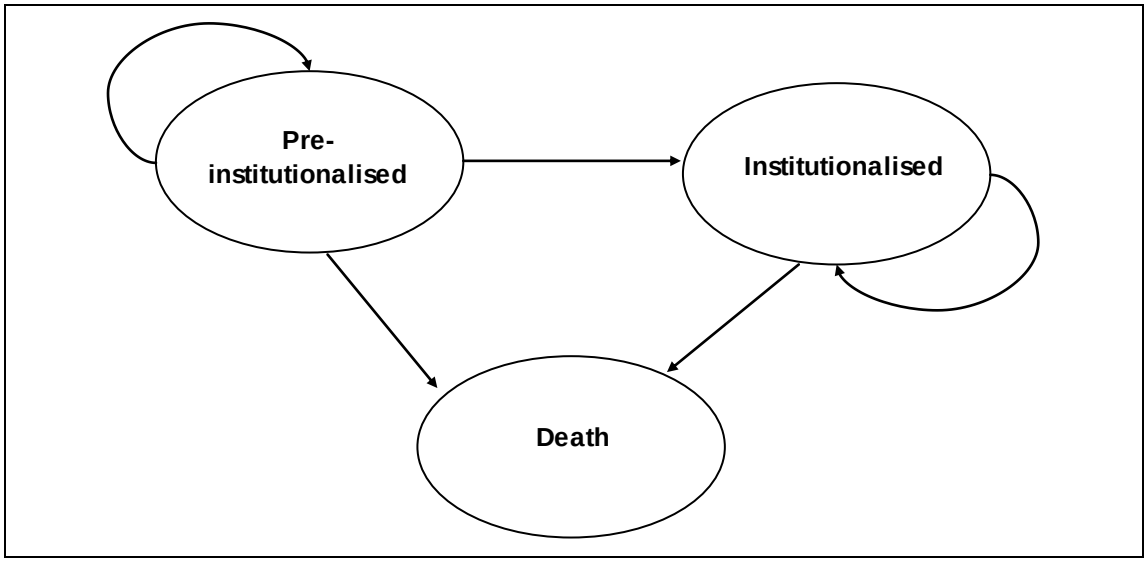
Model structure

The Assessment Group evaluated the cost effectiveness of the AChE inhibitors and memantine over a lifetime (20-year) time horizon. The Assessment Group constructed a Markov model that estimated the time to institutionalisation, which was defined as 'living in a residential home or a nursing home (not short respite care) or in a hospital on a long-term or permanent basis'. The model included three health states: pre-institutionalisation, institutionalisation and death. Depending on the severity of Alzheimer's disease at the beginning of the model, people could enter the model in the pre-institutionalised or institutionalised health state. Institutionalisation was equivalent to severe Alzheimer's disease (MMSE ≤ 10) at which point treatment with an AChE inhibitoris stopped in line with the marketing authorisation. Individual patients' data were used to estimate the proportion of the total cohort in each state at the end of each monthly cycle. An exponential survival regression model was fitted with time to end of pre-institutionalisation (considering early death) as the response variable and MMSE, Barthel-ADL and age at start of study as covariates. The model incorporated a gradual increase in the costs and gradual reduction in the health-related quality of life with time. Cost and benefits were discounted at a rate of 3.5%.

Because of differences in the marketing authorisations of the technologies there were several decision problems to be addressed (see table 103, page 256 of the assessment report). Therefore, the cost effectiveness of AChE inhibitors and memantine were modelled separately. The base case model for

AChE inhibitors followed a cohort of 1000 individuals with mild to moderate (MMSE 26–10) Alzheimer's disease for which the comparators were donepezil, rivastigmine (patch and capsule), galantamine and best supportive care. The base-case model for memantine followed a cohort of 1000 individuals with moderate to severe (MMSE 20–0) Alzheimer's disease, for which the comparator was best supportive care. The Assessment Group used a prevalent cohort approach. Populations with mild, moderate and severe disease were assessed individually in the sensitivity analyses (see table 103 in the assessment report). Due to the lack of available evidence on the rate of discontinuation, a constant rate of 4% discontinuation per cycle for all drugs at all doses was assumed. Therefore within 25 months all patients were assumed to have stopped treatment.

Figure 2 Diagram of the structure of the Assessment Group Markov model



Source: Figure 59, page 265 assessment report

The model assumed that people had been diagnosed with Alzheimer's disease for a median of 4.0 years and a mean of 4.9 years. Patient characteristics (cognition [MMSE] and function [the Barthel Index of activities of daily living] with three subgroups defined by age) were based mainly on individual patients' data from a community-based cohort study of people with untreated Alzheimer's disease by Wolstenholme and colleagues in

Oxfordshire (n = 92). Data from the LASER-AD study were used to predict the proportion of patients who, at the start of the decision model, were in the institutional care health state (10% for the mild to moderate cohort and 40% for the moderate to severe cohort, based on 5.6% of people with MMSE ≥ 19, 27.1% of people with MMSE 15–19 and 59% people with MMSE < 19 as reported in the LASER-AD study). Further information on patient characteristics in the Wolstenholme study can be found in table 105, page 267 of the assessment report.

In the base-case analysis, it was assumed that treatment delayed time to institutionalisation but not to death. Time to death was predicted by age, cognition (MMSE) and function (activities of daily living).

Model inputs

Estimates of treatment effect (MMSE and ADCS-ADL, in particular) taken from the placebo-controlled randomised controlled trials identified in the systematic review of clinical effectiveness were applied to baseline estimates for best supportive care. Estimates of clinical effectiveness (table 8) were slightly different to those in the clinical effectiveness section of the assessment report as only randomised controlled trials of licensed doses were considered. Rivastigmine patches were considered separately to capsules because of the different effectiveness profiles.

Table 8 Estimates of effectiveness (at 6 months) used in the Assessment Group decision model

	Outcome measure	WMD	Analysis type	Source
Donepezil (10 mg)	MMSE	1.24 (95% CI 0.81 to 1.66)	M-A result	AD 2000 (2004), Rogers et al (1998), Gauthier et al (2002), Seltzer et al (2004), Mohs et al (2001), Winblad et al (2001) appendix 5, figure 15.
	ADCS-ADL	2.02 (95% CI 1.06 to 3.28)		Average of estimate from galantamine (24 mg) and rivastigmine (≤ 12 mg).
	ADAS-cog	−2.90 (95% CI −3.61 to −2.18)	M-A result	
Galantamine (16–24 mg)	MMSE	1.13 (95% CI 0.72 to 1.54)		Average of donepezil (10 mg) and rivastigmine (≤ 12mg).
	ADCS-ADL	2.23 (95% CI 1.33 to 3.14)	M-A result	Tariot et al (2000), Brodaty et al (2005).
	ADAS-cog	−3.05 (95% CI −3.52 to −2.57)	M-A result	
Rivastigmine capsules (9–12 mg)	MMSE	1.02 (95% CI −0.63 to 1.41)	M-A result	Feldman & Lane (2007), Winblad et al (2007).
	ADCS-ADL	1.80 (95% CI 0.20 to 3.40)	Single study	Winblad et al (2007).
	ADAS-cog	−2.34 (−3.38 to 1.30)	M-A result	
Rivastigmine patches (10 cm²)	MMSE	1.10 (95% CI 0.52 to 1.68)	Single study	Winblad et al (2007).
	ADCS-ADL	2.20 (95% CI 0.62, 3.78)	Single study	Winblad et al (2007).
	ADAS-cog	−1.60 (95% CI −2.73 to −0.47)	Single study	Winblad et al (2007).
Memantine (15–20 mg)	MMSE	0.70 (95% CI 0.02 to 1.38)	Single study	Reisberg et al (2003). Note: only data from memantine versus placebo randomised controlled trials.
	ADCS-ADL	1.41 (95% CI 0.04 to 2.78)	M-A result	Reisberg et al (2003), Van Dyck et al (2007) Note: only data from memantine versus placebo randomised controlled trials.

Source: table 108, p278 of the assessment report

ADAS-cog = Alzheimer's Disease Assessment Scale – cognitive subscale. ADAS-ADL = Alzheimer's disease Cooperative Studies – Activities of Daily Living. CI = Confidence interval. M-A = meta-analysis, MMSE = Mini Mental State Examination. WMD = weighted mean difference

The assessment report noted literature highlighting that patients self-report much higher utilities than those estimated by carers, particularly in people with severe Alzheimer's disease. The base-case model included patient utilities based on carer-proxy utility values because of better consistency of results (table 9). Self reported patient utility, and carer utility was included in sensitivity analysis. Carer utility associated with caring for patients with different CDR severities of Alzheimer's disease was mapped onto the MMSE scale. The utility of caring with someone with mild dementia (MMSE 21–25) was 0.87 which was reduced to 0.86 when caring for someone with severe dementia (MMSE of less than 10).

Table 9 Utilities used in the base-case analysis of the Assessment Group model

Health state	Value	n	Assessment Group estimates of standard deviation	Patient rated quality of life
Pre-institutionalization by MMSE				
0-9	0.33	44	0.151	0.78
10-14	0.49	88	0.107	0.73
15-20	0.5	83	0.110	0.83
21-25	0.49	25	0.200	0.85
26-30	0.69	22	0.213	0.84
Institutionalisation (MMSE 0–9)	0.33	44	0.151	0.78
Dead	0			
Source: table 111, page 297 of the assessment report; from Jonsson and colleagues. MMSE = Mini Mental State Examination.				

Note that no estimates of uncertainty were reported by Jonsson and colleagues; only the number of carers contributing to the mean estimate. Resource use was estimated from the Wolstenholme cohort study. The monthly drug costs based on British National Formulary (BNF) 58 ranged from £71 with memantine to £98 for rivastigmine capsules. The cost of outpatient visits was assumed to be £26 per month and £158 for a 6-monthly assessment. The overall mean monthly cost of institutionalised care was estimated as £2941 (28% of which was assumed to be self-funded) and the cost of pre-institutionalised care was dependant on the severity of disease

and the time to institutionalisation (for example, 1 year before institutionalisation the mean monthly costs for people with mild to moderate Alzheimer's disease was £1938 per month compared with £2427 per month for people with moderate to severe Alzheimer's disease. No adverse events or carer costs were included in the economic model.

Key assumptions in the base-case analysis are described by the Assessment Group on page 311 of the assessment report. A summary of the parameter values of the base-case model can be found in table 114 (pages 307311 of the assessment report).

Results of the Assessment Group model

The Assessment Group presented the deterministic ICERs and one-way sensitivity analysis (which included an analysis of the robustness of the ICER to different structural assumptions) and the probabilistic ICERs (which represent the combined effect of some of the parameter uncertainties in the model) for each of the technologies.

Cost effectiveness of an AChE inhibitor (mild to moderate base-case in the Assessment Group model)

The deterministic model estimates that treatment with an AChE inhibitor delays time to institutional care by between 10 and 12 days. The gain of increased time in the pre-institutional state is small compared with the increased costs of treatment. Base-case ICERs are shown in table 10.

Table 10 Base-case ICERs[a] from the Assessment Group model for AChE inhibitors in people with mild to moderate Alzheimer's disease

	Deterministic[b]	Probabilistic[b]	Deterministic versus best supportive care
Rivastigmine patches (10 cm²)	£61,100	£59,800	£61,100
Galantamine (16–24 mg)	£151,100	£157,800	£62,700
Donepezil (10 mg)	Dominated	Dominated	£80,400
Rivastigmine capsules (9–12 mg)	Dominated	Dominated	£100,600

ICER = Incremental cost effectiveness ratio.

[a] Rounded to nearest £100.

[b] Compared with next cheapest, non-dominated treatment option.

The Assessment Group conducted univariate sensitivity analysis to assess the sensitivity of the ICER to different parameters. The deterministic ICER was not sensitive to most of the one-way sensitivity analyses. When cognition benefits were measured using ADAS-cog, galantamine dominated all other treatments and had an ICER of £58,400 per QALY gained compared with best supportive care. When a survival benefit of treatment was assumed, the ICER for rivastigmine patches compared with best supportive care was £72,200 per QALY gained and the ICER of galantamine compared with rivastigmine patches was £101,600 per QALY gained. For further information please refer to tables 118 and 119 on pages 324 and 327 of the assessment report.

Probabilistic sensitivity analyses of the cost effectiveness of oral AChE inhibitors show that at a threshold of £30,000 per QALY gained best supportive care had the highest probability (57%) of being cost effective followed by rivastigmine patches (10 cm^2), which were the next most likely cost effective option in 17% of the analyses.

Cost effectiveness of memantine (moderate to severe base-case in the Assessment Group model)

The deterministic model showed that treatment with memantine delays time to institutional care by about 6 days. The base-case results are shown in table 11.

Table 11. Assessment Group base-case deterministic results for people with moderate to severe Alzheimer's disease (MMSE 20–0)

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[a]
Best supportive care	£78,136	1.214			
Memantine (20 mg)	£78,855	1.217	£719	0.003	£248,500

MMSE = Mini Mental State Examination. ICER = Incremental cost effectiveness ratio. QALY = Quality-adjusted life year.

[a] Cost per QALY rounded to the nearest £100.

Probabilistic sensitivity analysis of the cost effectiveness of memantine in the population with moderate to severe Alzheimer's disease estimated a probability of memantine being more cost effective than best supportive care of less than 4% at a threshold of £30,000 per QALY gained.

The Assessment Group conducted one-way sensitivity analysis to assess the sensitivity of the ICER to different parameters. When a treatment effect on survival was assumed the ICER of memantine compared with best supportive care was £107,900 per QALY gained.

Summary of the Assessment Group model results

The Assessment Group considered that the ICERs generated by its model should be interpreted with caution in light of the very small incremental costs and benefits and the considerable parameter and structural uncertainty in the model. Parameters that had the most effect on the ICERs of the AChE inhibitors were survival effect, the Barthel and MMSE coefficients in the equations predicting time to institutionalisation (the extent to which cognition and functional ability predict time to institutionalisation), treatment discontinuation, cost of institution, utility estimates and carers' quality of life.

Similar results for the one-way sensitivity analysis of memantine showed that none of the alternative assumptions assessed led to a positive net benefit for memantine compared with best supportive care at a threshold of £30,000 per QALY.

Subgroup analyses conducted by the Assessment Group

The Assessment Group conducted analyses of the individual mild, moderate and severe populations. The ICERs are shown in table 12 for each technology compared with the next cheapest, non-dominated technology and are rounded to the nearest £100. The Assessment Group highlighted that caution should be taken when assessing these results as effectiveness estimates are derived from trials that include populations with varying severity of disease. Table 12 is tables 125–7 from pages 345-349 of the assessment report.

Table 12 Assessment Group cost–utility results of drugs for subgroups according to severity of Alzheimer's disease

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[ab]
Mild Alzheimer's disease					
Best supportive care	£75,515	1.749			
Rivastigmine patch (10 cm²)	£76,068	1.755	£553	0.007	£81,700
Galantamine (16–24 mg)	£76,092	1.756	£24	0.0001	£178,000
Donepezil (10 mg)	£76,210	1.756	Dominated		
Rivastigmine capsules (9–12 mg)	£76,261	1.755	Dominated		
Moderate Alzheimer's disease					
Best supportive care	£67,536	1.500			
Rivastigmine patch (10 cm²)	£67,999	1.508	£463	0.008	£58,000
Galantamine (16–24 mg)	£68,021	1.508	£22	0.0002	£147,900
Donepezil (10 mg)	£68,145	1.508	Dominated		
Rivastigmine capsules (9–12 mg)	£68,198	1.507	Dominated		
Memantine (15–20 mg)	£68,069	1.505	Dominated		
Severe Alzheimer's disease					
Best supportive care	£67,993	1.012			
Memantine (15–20 mg)	£68,694	1.014	£701	0.003	£279,700

ICER = Incremental cost-effectiveness ratio. QALY = Quality-adjusted life year.
[a] Cost per QALY rounded to the nearest £100.
[b] Compared to next cheapest, non-dominated technology

Subgroup analyses for starting populations with mild or moderate Alzheimer's disease had little effect on the base-case ICERs in which rivastigmine patches remained the most cost-effective option followed by galantamine which dominated the other technologies. Memantine had a higher ICER of £279,700 in severe disease.

Comparison of the Assessment Group and the SHTAC (2004) models

The Assessment Group considered the improvements of its model compared with the previous SHTAC model to be that costs and utilities were varied according to time before institutionalisation and UK rather than US data were used to model disease progression. The Assessment Group noted some limitations of its model. These were that it assumed a treatment benefit on

cognition and function but not on behavioural and psychological symptoms, the expression of treatment effectiveness was mainly based on delay in time to institutionalisation, changes in cost and utility before institutionalisation were assumed to be delayed by the same amount of time as institutionalisation, and the uncertain generalisability of the Wolstenholme cohort to the UK population. Full treatment effect at 6 months was also assumed. The Assessment Group presented the deterministic ICER for each treatment compared with best supportive care so that it is comparable with the data presented in NICE technology appraisal guidance 111.

Table 13 ICERs[a] from the Assessment Group model and the SHTAC model for AChE inhibitors compared with best supportive care in people with mild to moderate Alzheimer's disease

	Donepezil (10 mg)	Galantamine (16–24 mg)	Rivastigmine capsules (9–12 mg)	Rivastigmine patches (10 cm²)b
Assessment Group model (deterministic base-case results	£80,400	£62,700	£100,600	£61,100
NICE technology appraisal guidance 111 monograph	£80,900	£68,000	£58,000	
SHTAC model updated with Assessment Group assumptions (3.5% discount rates; probabilities; 20 year time horizon)	£66,500	£55,000	£46,100	
As previous row plus discontinuations and Assessment Group effectiveness and cost estimates	£45,300	£37,700	£72,200	

Source: table 129, page 350 of the assessment report

AChE = Acetylcholinesterase. ICER = Incremental cost effectiveness ratio. SHTAC = Southampton Health Technology Assessment Centre.

[a] Rounded to nearest £100.

[b] Only rivastigmine capsules were evaluated in the SHTAC model, not the patches.

The ICERs produced by the Assessment Group model (drugs compared with best supportive care) of approximately £80,400 per QALY gained for donepezil and £248,500 for memantine were very different from those submitted by the manufacturers (in which treatment with AChE inhibitors or memantine dominated best supportive care) but are similar to the ICERs in

NICE technology appraisal guidance 111 (table 13). When the Assessment Group applied assumptions of 3.5% discount to costs and benefits and when probabilities were correctly applied along with a 20-year time horizon, the ICERs for each of the technologies were reduced (see table 13). The clinical effectiveness of treatments and costs estimates used in the Assessment Group model were less than the SHTAC model (see table 130, page 351 of the assessment report). When effectiveness and cost estimates of the Assessment Group model were also applied to the SHTAC model this further reduced the ICER. This is presented in table 13.

These differences may be accounted for by the following:

- Patient characteristics in the SHTAC model were based on US data (n = 236), in which a number of different domains (ADAS-cog, psychiatric symptoms, extrapyramidal symptoms, age of onset and duration of illness) affected the time to institutionalisation compared with the Assessment Group model, which was based on UK data (n = 92) and assumed that age and MMSE predicted institutionalisation.
- The Assessment Group model estimated less difference in the cost of care (increase of £283 with drug treatment in the pre-institutionalised health state and a cost saving of £647 in the institutionalised health state) than the SHTAC model (increase of £4315 with drug treatment for the pre-institutionalised health state and a cost saving of £4531 in institutionalised health state).
- The Assessment Group assumed less of a treatment effect for an AChE inhibitor, which translates to a much shorter delay to full-time care or institutionalisation (2 months in the SHTAC model compared with 11 days in the Assessment Group model (see table 131 on page 352 of the assessment report).

- The results of the models differ in the time spent in the institutionalised or full-time care states which consequently affects costs.

Comparison of the Assessment Group and donepezil manufacturer's model (mild to moderate Alzheimer's disease)

The manufacturers of donepezil modelled the cost effectiveness of donepezil treatment compared with best supportive care. The manufacturer of donepezil reported that donepezil treatment dominated best supportive care for both the mild and moderate populations compared with the Assessment Group model which reported an ICER of £102,000 in mild disease and £77,400 in moderate disease for donepezil compared with best supportive care. A comparison is shown in tables 14 and 15.

Table 14 Results from the manufacturer and Assessment Group models for donepezil in mild disease[a]

		Model outputs (mild)		Incremental values	
Output	**Treatment**	**Manufacturer of donepezil**	**Assessment Group**	**Manufacturer of donepezil**	**Assessment Group**
ICER		Donepezil dominates	£101,703		
Total costs	Donepezil	£79,023	£76,210		
	No treatment	£82,409	£75,515	−£3386	£695
Total QALYs	Donepezil	4.267 (patient + carer)[b]	1.756 (patient only)		
	No treatment	4.120 (patient and carer)	1.749 (patient only)	0.147	0.007

ICER = Incremental cost effectiveness ratio. QALY = Quality-adjusted life year.

[a] All costs and QALYs discounted.

[b] Eisai/Pfizer base case includes carer QALYs, therefore total QALYs = patient QALYs + carer QALYs. Donepezil total QALYs = 1.502 + 2.765. No treatment total QALYS = 1.370 + 2.750.

Table 15 Results from the manufacturer and Assessment Group models for donepezil in moderate disease[a]

		Model outputs (moderate disease)		Incremental values	
Output	**Treatment**	**Manufacturer of donepezil**	**Assessment Group**	**Manufacturer of donepezil**	**Assessment Group**
ICER		Donepezil dominates	£77,428		
Total costs	Donepezil	£102,086	£68,145		
	No treatment	£103,969	£67,536	−£1883	£609
Total QALYs	Donepezil	4.353 (patient + carer)[b]	1.508 (patient only)		
	No treatment	4.245 (patient + carer)[b]	1.500 (patient only)	0.108	0.008

ICER = Incremental cost effectiveness ratio. QALY = Quality-adjusted life year.

[a] All costs and QALYs discounted.

[b] Eisai/Pfizer base-case includes carer QALYs, therefore, total QALYs = patient QALYs + carer QALYs. Donepezil total QALYs = 1.332 + 3.021. No treatment total QALYS = 1.234 + 3.011.

Differences between the results of Assessment Group and manufacturer's models may be accounted for by the following:

- The donepezil manufacturer's model estimated longer overall survival (4.6 undiscounted life years for the moderate cohort) compared with the Assessment Group model (3.36 years).
- The donepezil manufacturer's model estimated people would spend less time living in the community (40% compared with 64% of the remaining lifetime in the Assessment Group model) and more time in institutional care which leads to a higher cost of care in the best supportive care arm.
- The donepezil manufacturer's model assumed a greater treatment effect than in the Assessment Group model.
- Difference in calculation of pre-institutionalisation cost (MMSE in the donepezil model compared with time to institutionalisation in the Assessment Group model)
- Differences in the cost of institutional care (£2801 per month in the donepezil model compared with £2117 in the Assessment Group model).

- Different utility – patients only in the Assessment Group versus patient and carer in the model by the manufacturer of donepezil.
- The donepezil submission assumed that 100% of the costs of care were funded by the NHS and PSS. The Assessment Group conducted a sensitivity analysis that used the costs of care in the donepezil submission, which reduced the base-case ICER from £77,400 to £28,600 for the population with moderate disease.

Comparison of the Assessment Group and memantine manufacturer's model (moderate to severe Alzheimer's disease)

One of the main differences between the manufacturer's model of memantine and the Assessment Group model was that treatment was assumed to continue in institutionalisation by the Assessment Group but not the manufacturer of memantine (table 135 in the assessment report). The cost-effectiveness model submitted by the manufacturer of memantine reported that treatment with memantine dominates best supportive care.

The Assessment Group model, however, estimated an ICER of £103,900 per QALY gained for a cohort with moderate Alzheimer's disease. The ICER for a cohort with severe disease was above £53,000 per QALY gained in the previous model for NICE technology appraisal guidance 111.

Table 16 Deterministic model outputs from Assessment Group and manufacturer of memantine models

		Model outputs (moderate to severe)		Incremental values	
Output	**Treatment**	**Manufacturer of memantine**	**Assessment Group**	**Manufacturer of memantine**	**Assessment Group**
ICER		Memantine dominates	£103,885		
Total costs	Memantine	£93,076	£68,069		
	No treatment	£94,787	£67,536	−£1711	£533
Total QALYs	Memantine	1.533	1.505		
	No treatment	1.502	1.500	0.031	0.005
ICER = Incremental cost effectiveness ratio. QALY = Quality adjusted life year.					

The estimated overall survival was similar in the two models (3.7 years in the manufacturer of memantine's model and 3.6 years in the Assessment Group model).

The key difference between the models is that the manufacturer's model assumes a greater treatment effect with memantine, which translates to a delay to entering full-time care of 1 month compared with a delay of 7 days estimated by the Assessment Group model. Higher costs are attributed to the full-time care state in the manufacturer's model (£3267 compared with £2117 in the Assessment Group model). The manufacturer's model also assumed a higher cost of, and a shorter time in, pre-institutional care with treatment in the manufacturer's model (1.73 years in the memantine model compared with 2.3 years in the Assessment Group model). When the Assessment Group conducted a sensitivity analysis that used the cost assumptions of the manufacturer of memantine's model (institutional care cost of £3267 per month and £724 for pre-institutional care) the ICER decreased to £49,563 per QALY gained from £103,900.

4 Equality issues

NICE technology appraisal guidance 111 acknowledges the equality issues in relation to the using the MMSE instrument alone as a measure of severity in particular groups. This includes people with learning or other disabilities, linguistic or other communication difficulties, or if applying the MMSE in a language in which the patient is sufficiently fluent is not possible.

5 Issues for consideration

Clinical effectiveness

Has the clinical need of patients and availability of alternative treatments changed since NICE technology appraisal guidance 111 was published in 2004?

Has the evidence of clinical effectiveness changed since 2004 in terms of cognition, function, behaviour and global outcomes?

Has the evidence of adverse effects changed since 2004?

What is the Committee's view on the availability, nature and quality of the new evidence?

- To what extent does the absence of health-related quality of life evidence impact on estimates of clinical and cost effectiveness for AChE inhibitors and memantine?
- Should non-RCT evidence (prospective longitudinal studies, observational data) be considered in order to fill the gaps in the evidence (e.g. longer-term data, carer impact and burden)?

What are the most plausible estimates of the size of clinical effectiveness including strength of all supporting evidence?

Is there evidence of differential effectiveness in clinically relevant subgroups (e.g severity, aggression/agitation and/or psychiatric symptoms)?

Does evidence show that adding memantine to stable dose AChE inhibitors is clinically effective compared with monotherapy?

Are there any new equality and diversity considerations?

Cost effectiveness

Modelling disease progression and treatment effect

- Have the appropriate measures of disease progression and treatment effect (e.g. cognition, function, behaviour, age, gender or other factors) been included?

- Is the selection of data to model disease progression (Oxfordshire, LASER-AD, CERAD cohort studies) appropriate and generalisable to the current UK Alzheimer's population?
- What is the most relevant data to estimate treatment effect in the models?
- Is one model type more appropriate than another for modelling Alzheimer's disease (e.g. discrete event simulation, Markov modelling, individual patient sampling or cohort modelling)?
- Do the states or events in the models (e.g. pre and post-institutionalisation or full-time care, stopping treatment or GP visits) provide an adequate framework to capture the impact of treatment on costs and health-related quality of life?
- Does modelling disease progression and treatment effect based on time to institutionalisation impact on the evaluation of cost effectiveness for memantine in a different way to AChE inhibitors?
- Is there any evidence to inform assumptions about the influence of disease or treatment on mortality?
- Have appropriate assumptions about treatment duration been made (stopping AChEI on institutionalisation as assumed to be equivalent to severe, continuation of memantine until death)?
- Are the assumptions about delay of treatment effect and continuation of following treatment cessation appropriate?
- Are the assumptions of treatment effect in subgroups of people with mild, moderate or severe Alzheimer's disease appropriate?
- Have appropriate discontinuation rates been included?

Costs

- Have appropriate assumptions been made in establishing up-to-date cost estimates?
- Are the assumptions about costs of monitoring appropriately modelled (GP versus specialist monitoring)?
- Has the variation in resource use and costs over time prior to institutionalisation or full-time care been appropriately modelled?
- Has the private funding of institutional or full-time care been appropriately captured in the models?

Health-related quality of life (utility values)

- Has the change in patient and carer utility prior and post institutionalisation or full-time care been appropriately modelled?
- Have measures of patient and carer utility been appropriately incorporated (the inclusion of proxy carer utility values for patients, mapping of health outcomes to obtain utility values)?
- Is it appropriate to assume that patient's health-related quality of life and utility once in an institution are assumed to be equivalent to be that of people with severe Alzheimer's disease?

Comparison of model results

- What factors are driving estimates of cost effectiveness and the differences between the different model outputs?
- Which are the most plausible estimates of cost effectiveness?

Is the technology particularly cost effective for specific groups of people (for example, people with mild, moderate, severe Alzheimer's disease or the subgroup with behavioural symptoms)?

6 Ongoing research

The MAG-D (memantine for agitation in dementia) study including memantine is due to publish initial data in the near future.

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by PenTAG:

> Bond M, Rogers G, Peters J et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model, June 2010.

B Submissions or statements were received from the following organisations:

Manufacturers/sponsors:

- Eisai and Pfizer
- Lundbeck
- Shire

Professional/specialist, patient/carer and other groups:

- Alzheimer's Society
- British Geriatric Society
- The Research Institute for the Care of Older People
- The Royal College of Psychiatrists

Appendix B: The recommendations of NICE technology appraisal guidance 111 (2004)

1 Guidance

This guidance applies to donepezil, galantamine, rivastigmine and memantine within the marketing authorisations held for each drug at the time of this appraisal; that is:

- donepezil, galantamine, rivastigmine for mild to moderately severe Alzheimer's disease
- memantine for moderately severe to severe Alzheimer's disease.

The benefits of these drugs for patients with other forms of dementia (for example, vascular dementia or dementia with Lewy bodies) have not been assessed in this guidance.

1.1 The three acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine are recommended as options in the management of patients with Alzheimer's disease of moderate severity only (that is, subject to section 1.2 below, those with a Mini Mental State Examination [MMSE] score of between 10 and 20 points), and under the following conditions:

- Only specialists in the care of patients with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of the elderly) should initiate treatment. Carers' views on the patient's condition at baseline should be sought.
- Patients who continue on the drug should be reviewed every 6 months by MMSE score and global, functional and behavioural assessment. Carers' views on the patient's

condition at follow-up should be sought. The drug should only be continued while the patient's MMSE score remains at or above 10 points (subject to section 1.2 below) and their global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect. Any review involving MMSE assessment should be undertaken by an appropriate specialist team, unless there are locally agreed protocols for shared care.

When using the MMSE to diagnose moderate Alzheimer's disease, clinicians should be mindful of the need to secure equality of access to treatment for patients from different ethnic groups (in particular those from different cultural backgrounds) and patients with disabilities.

1.2 In determining whether a patient has Alzheimer's disease of moderate severity for the purposes of section 1.1 above, healthcare professionals should not rely, or rely solely, upon the patient's MMSE score in circumstances where it would be inappropriate to do so. These are:

- where the MMSE is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient's dementia because of the patient's learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties **or**
- where it is not possible to apply the MMSE in a language in which the patient is sufficiently fluent for it to be an appropriate tool for assessing the severity of dementia, or there are similarly exceptional reasons why use of the MMSE, or use of the MMSE by itself, would be an inappropriate tool for assessing the severity of dementia in that individual patient's case.

In such cases healthcare professionals should determine whether the patient has Alzheimer's disease of moderate severity by making use of another appropriate method of assessment. For the avoidance of any doubt, the acetylcholinesterase inhibitors are recommended as options in the management of people assessed on this basis as having Alzheimer's disease of moderate severity.

The same approach should apply in determining for the purposes of section 1.1 above, and in the context of a decision whether to continue the use of the drug, whether the severity of the patient's dementia has increased to a level which in the general population of Alzheimer's disease patients would be marked by an MMSE score below 10 points.

1.3 When the decision has been made to prescribe an acetylcholinesterase inhibitor, it is recommended that therapy should be initiated with a drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative acetylcholinesterase inhibitor could be prescribed where it is considered appropriate having regard to adverse event profile, expectations around concordance, medical comorbidity, possibility of drug interactions and dosing profiles.

1.4 Memantine is not recommended as a treatment option for patients with moderately severe to severe Alzheimer's disease except as part of well-designed clinical studies.

1.5 Patients with mild Alzheimer's disease who are currently receiving donepezil, galantamine or rivastigmine, and patients with moderately severe to severe Alzheimer's disease currently receiving memantine, whether as routine therapy or as part of a clinical trial, may be continued on therapy (including after the

conclusion of a clinical trial) until they, their carers and/or specialist consider it appropriate to stop.