Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and memantine for Alzheimer’s disease: systematic review and economic model†

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Abstract

Introduction: in 2007 the National Institute of Health and Clinical Excellence (NICE) restricted the use of acetylcholinesterase inhibitors and memantine.

Methods: we conducted a health technology assessment (HTA) of the effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of AD to re-consider and update the evidence base used to inform the 2007 NICE decision. The systematic review of effectiveness targeted randomised controlled trials. A comprehensive search, including MEDLINE, Embase and the Cochrane Library, was conducted from January 2004 to March 2010. All key review steps were done by two reviewers. Random effects meta-analysis was conducted. The cost-effectiveness was assessed using a cohort-based model with three health states: pre-institutionalised, institutionalised and dead. The perspective was NHS and Personal Social Services and the cost year 2009.

Results: confidence about the size and statistical significance of the estimates of effect of galantamine, rivastigmine and memantine improved on function and global impact in particular. Cost-effectiveness also changed. For donepezil, galantamine and rivastigmine, the incremental cost per quality-adjusted life year (QALY) in 2004 was above £50,000; in 2010 the same drugs ‘dominated’ best supportive care (improved clinical outcome at reduced cost). This was primarily because of changes in the modelled costs of introducing the drugs. For memantine, the cost-effectiveness also improved from a range of £37–53,000 per QALY gained to a base-case of £32,000.

Conclusion: there has been a change in the evidence base between 2004 and 2010 consistent with the change in NICE guidance. Further evolution in cost-effectiveness estimates is possible particularly if there are changes in drug prices.

Keywords: Alzheimer’s disease, donepezil, galantamine, rivastigmine, memantine, systematic review, older people

Introduction

Alzheimer’s disease (AD), the most commonly occurring form of dementia, is a major challenge to public health.

A number of different staging and screening tools are used in the assessment of presence and severity of cognitive decline accompanying the disease, but commonly AD is divided into differing severities by the Mini-Mental State Examination (MMSE) score [1]. From a possible score of 30, <10 is indicative of severe AD; 10–20 of moderate and 21–26 of mild.

There are currently no cures for AD and the inexorable impact of the disease on patient and carers generates great...
pressure to ensure that any potential treatments are widely available. The options for intervention in the course of the disease are limited but two groups of drugs have become licensed for treatment [2]:

- Acetylcholinesterase inhibitors (AChEI) (donepezil, galantamine and rivastigmine).
- N-methyl-D-aspartate receptor antagonists, particularly memantine.

AD is characterised by a cerebral cholinergic deficit as a consequence of the pathological changes. The AChEIs are reversible non-competitive inhibitors of acetylcholinesterase that act to raise the concentration of acetylcholine in brain synapses by preventing its breakdown. Memantine inhibits the destructive effect of an excessive excitatory action of glutamate seen in AD by reversible antagonism of N-methyl-D-aspartate receptors. The AChEIs have marketing authorisations in the UK for the treatment of adults with moderate and mild AD (MMSE score 10–26), whereas memantine has a UK licence for the treatment of people with moderate and severe AD (MMSE score 20 or less). The main proposed benefits of the drugs are improved cognition, function and behaviour, which may lead in turn to an ability to remain independent and self-caring for longer. There are side-effects which may limit the ability of patients to take the drugs. In the case of AChEIs, these include slowing of heart rate, nausea, vomiting and dizziness. For memantine, they include dizziness, headache, confusion and incontinence.

The costs of the drugs are in the region of £50–100 per patient per month, depending on the precise drug, preparation, dose and locally negotiated discounts; these are modest relative to many other new drugs [2]. Total budget impact may still be problematic for commissioners because of the relatively large number of people affected and the possibility that treatment will continue for several years. A UK survey suggests that a typical half million general population may contain 6,500 cases of dementia [3] some of whom will not be identifiable at present because early diagnosis may be viewed as unhelpful in the absence of clear treatment options.

In 2004 NICE began appraisal of the four drugs. In 2007, after protracted debate, an appeal process and a judicial review, NICE issued final guidance restricting access in the NHS in England and Wales to the AChEIs and memantine on the grounds of unfavourable cost-effectiveness, compounded in the case of memantine by uncertainty about its effectiveness [4]. AChEIs were approved for moderate AD (MMSE score 10–20) and memantine was only recommended as part of a well designed clinical study. In 2010 NICE undertook a planned up-dating of its guidance which now allows the use of AChEIs in all the licensed severities of AD, extending its use from moderate into mild disease (MMSE score 21–26), and memantine into routine clinical practice [5]. Although generally welcomed, there have been suggestions that the evidence base has changed little since the original guidance and the decision is politically expedient representing capitulation to pressure from the media, pharmaceutical companies and patient interest groups [6].

This study examines whether and how the evidence has changed between 2004 and 2010.

**Methods**

We conducted a health technology assessment (HTA) of the effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of AD. The interventions were the drugs at the doses given in the UK licence. The normal doses of the tablet formulations are donepezil 5–10 mg once daily, galantamine 16–24 mg once daily, rivastigmine 1.5–6 mg twice daily and memantine 5–20 mg once daily. For AChEIs, the population of interest was mild and moderate AD (MMSE score 10–26) and for memantine it was moderate and severe AD (MMSE score 20 or less). The comparator was generally best supportive care (BSC) alone. For mild AD (MMSE score 21–26) any AChEI could also be compared with another and for moderate AD (MMSE score 10–20) any AChEI or memantine could also be compared with one another. The only comparison in the severe AD group (MMSE score <10) was memantine with BSC against BSC alone. The outcomes of particular interest were severity of disease and response to treatment, behavioural symptoms, mortality, ability to remain independent, likelihood of admission to residential/nursing care, health-related quality of life of patients and carers, adverse effects of treatment, cost-effectiveness and costs.

The main components of the HTA were a systematic review of effectiveness, a systematic review of cost-effectiveness, a critical appraisal of industry submissions and an original health economic model of cost-effectiveness. Full details of the HTA methods are available in a technical report [7], but the key features of the two components directly relevant to this paper are given in the following paragraphs.

Systematic review of effectiveness: randomised controlled trials (RCTs) and systematic reviews of RCTs addressing the HTA question were sought. Electronic databases were searched from January 2004 to March 2010, in order to update previous searches. The databases searched included: the Cochrane Library (2009 Issue 4, CDSR and CENTRAL), MEDLINE, MEDLINE In Process, Embase, PsycINFO, EconLIT, ISI Web of Science Databases: Science Citation Index, Conference Proceedings Citation Index- and Biosis, the CRD databases: NHSEED, HTA and DARE databases. The meta-register of controlled trials and clinicaltrials.gov were searched for ongoing trials. Bibliographies of included studies and industry submissions (see below) were searched for further relevant studies. Study selection was performed independently by two reviewers with any disagreements being resolved by discussion. Quality assessment and data extraction were performed by a primary reviewer and checked by a second. Where data permitted, the results of individual trials were pooled using random effects meta-analyses because of the intrinsic clinical heterogeneity. This was done cumulatively adding the new studies to those in the original HTA [8]. Heterogeneity was examined by visualising the results and by
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reference to Cochran’s Q (compared with a \(\chi^2\) distribution) and the \(F\) statistics.

Original health economic model: this was developed from the structure used in the 2004 HTA [8]. A review of all documentation (from manufacturers, interest groups, NICE and the published literature) generated a list of key criticisms and perceived weaknesses. This was used to inform changes to the model structure and the parameter values (see Supplementary data available Age and Aging online, Table Appendix S1) for a new cohort-based model (PenTAG model) developed in Microsoft Excel 2007 with additional analyses in R. Three health states were used: ‘pre-institutionalised’ (largely independent), ‘institutionalised’ and ‘dead’. The economic perspective was NHS and Personal Social Services, the currency being GBP and the cost year 2009. A monthly time cycle was used with 20-year time horizon, by which time it was estimated that <5% of a cohort would be alive.

For each patient, the time until institutionalisation and time to death were independently estimated as functions of age, MMSE [1] and activities of daily living (ADL) score [9] based on a prevalent UK cohort of 92 AD patients from the study by Wolstenholme et al. (data followed from 1988 to 1999 in Oxfordshire) [10]. Estimates of the NHS and PSS costs associated with AD were taken from the same source. The effects of the drugs on MMSE and ADL were taken from the systematic review of effectiveness.

The PenTAG model starts when treatment begins. Mean time to institutionalisation and mean time to death are predicted using the mean baseline characteristics (age, MMSE and ADL) of the simulated cohort. The assumed effect of treatment with AChEIs or memantine is to delay institutionalisation compared with BSC alone, by improving MMSE and ADL scores. The magnitude of improvement in MMSE and ADL is drug specific, based on the results of the source RCTs at 6-month follow-up, corresponding to 6 months from the start of the model. The PenTAG model allows for treatment discontinuations, and also assumes that for the AChEIs treatment stops on institutionalisation (because the mean MMSE score at institutionalisation in the Oxfordshire study was <10). For memantine, treatment is not assumed to stop once individuals are in institutional care, although there is allowance for treatment discontinuations in the moderate to severe cohort.

The final step in the method was a comparison of the key findings from this HTA with the HTA which underpinned the NICE guidance in 2007 [8]. To facilitate comparison across the interventions, wherever possible changes in ADAS-COG were used as the measure of impact on behaviour, ADCS-ADL for function, NPI for behaviour and CIBIC-plus as the measure of global impact.

Results

A full table of all key clinical effectiveness estimates, modelled quality-adjusted life years (QALYs), modelled costs and incremental cost-effectiveness ratios (ICERs) from the HTA underpinning the 2007 NICE guidance [8] and our HTA is provided as Appendix S2 in the Supplementary data available Age and Aging online. Table 1 below summarises the findings emphasising changes in evidence.

Clinical effectiveness

The summary table indicates that there was the least additional information concerning the clinical effectiveness of donepezil between 2004 and 2010. The new review confirmed there were statistically significant benefits or trends towards benefit across all the main outcomes. There was an increase in the confidence about the beneficial effect on function (the new summary estimate had narrower confidence intervals which did not include 0). However, this was not due to the inclusion of a new small trial, but because fuller statistical information was available on the studies identified in 2004, which allowed a meta-analysis to be conducted (see Supplementary data available Age and Aging online, Table Appendix S2).

In the case of galantamine, there was new evidence since 2004 [11–13], but only one study randomising 971 patients contributed across all outcomes [11]. This, however, led to quantified and much more precise estimates of effect on function, behaviour and global impact, leading overall to much greater confidence about the beneficial effect. The beneficial effect of galantamine on cognition, established in 2004, was unchanged.

Similarly with rivastigmine there was new evidence [14–16], and the additional trials contributed across most of the outcomes. Again this led to quantified and much more precise estimates of effect on cognition, function and global impact, leading to much greater confidence about the beneficial effect of rivastigmine. Further this benefit occurred with the drug in the form of patches as well as tablets. The effect on behaviour remains uncertain.

With memantine there was also new evidence, with one new trial randomising 350 patients contributing across most outcomes [17]. However, the impact of this was offset by a change in synthesis methods: we believed that trials comparing memantine with placebo should not be combined with trials comparing an AChEI plus memantine with AChEI plus placebo. This led to the exclusion of one study which was originally included in 2004 [18]. Even so, quantified statistically significant benefit was apparent for function and global impact. In 2004 all of the observed trends in function and global impact could have been accounted for by chance alone.

An important general observation was that there was no new clinical effectiveness evidence on the impact on rates of, or time to institutionalisation.

Cost-effectiveness

There were also changes in the evidence on cost-effectiveness which were more marked than the changes in evidence on effectiveness. The new model suggested that
Table 1. Summary of effectiveness and cost-effectiveness for drugs for AD relative to BSC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Findings 2004</th>
<th>Findings 2010</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donepezil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>Quantified statistically significant benefit</td>
<td>Quantified statistically significant benefit</td>
<td>None</td>
</tr>
<tr>
<td>Function</td>
<td>Unquantified trend towards benefit</td>
<td>Quantified statistically significant benefit</td>
<td>More confidence about presence and size of benefit</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Unquantified trend towards benefit</td>
<td>Quantified statistically significant benefit</td>
<td>None</td>
</tr>
<tr>
<td>Global impact</td>
<td>Quantified statistically significant benefit</td>
<td>Quantified statistically significant benefit</td>
<td>None</td>
</tr>
<tr>
<td>Institutionalisation</td>
<td>Quantified trend towards benefit</td>
<td>Quantified trend towards benefit</td>
<td>None</td>
</tr>
<tr>
<td>Incremental QALYs</td>
<td>0.036</td>
<td>0.035</td>
<td>Costs associated with intervention decrease rather than increase</td>
</tr>
<tr>
<td>Incremental Costs</td>
<td>£2,895</td>
<td>−£588</td>
<td>Marked change in favour of intervention</td>
</tr>
<tr>
<td>ICER</td>
<td>£80,941 per QALY</td>
<td>£588</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Galantamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>Quantified statistically significant benefit</td>
<td>Quantified statistically significant benefit</td>
<td>None</td>
</tr>
<tr>
<td>Function</td>
<td>Unquantified trend towards benefit</td>
<td>Quantified statistically significant benefit</td>
<td>More confidence about presence and size of benefit</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Unquantified trend towards benefit</td>
<td>Quantified statistically significant benefit</td>
<td>None</td>
</tr>
<tr>
<td>Global impact</td>
<td>Unquantified trend towards benefit</td>
<td>Quantified statistically significant benefit</td>
<td>None</td>
</tr>
<tr>
<td>Institutionalisation</td>
<td>No empirical data</td>
<td>No empirical data</td>
<td>None</td>
</tr>
<tr>
<td>Incremental QALYs</td>
<td>0.039</td>
<td>0.033</td>
<td>Small decrease in modelled benefit</td>
</tr>
<tr>
<td>Incremental Costs</td>
<td>£2,648</td>
<td>−£520</td>
<td>Costs associated with intervention decrease rather than increase</td>
</tr>
<tr>
<td>ICER</td>
<td>£68,042 per QALY</td>
<td>−£20</td>
<td>Marked change in favour of intervention</td>
</tr>
<tr>
<td></td>
<td>Rivastigmine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>Unquantified trend towards benefit</td>
<td>Quantified statistically significant benefit</td>
<td>More confidence about presence and size of benefit</td>
</tr>
<tr>
<td>Function</td>
<td>Unquantified trend towards benefit</td>
<td>Quantified statistically significant benefit</td>
<td>None</td>
</tr>
<tr>
<td>Behaviour</td>
<td>No evidence of difference</td>
<td>Quantified statistically significant benefit</td>
<td>None</td>
</tr>
<tr>
<td>Global impact</td>
<td>Unquantified trend towards benefit</td>
<td>No evidence of difference</td>
<td>None</td>
</tr>
<tr>
<td>Institutionalisation</td>
<td>No empirical data</td>
<td>Quantified statistically significant benefit</td>
<td>None</td>
</tr>
<tr>
<td>Incremental QALYs</td>
<td>0.037</td>
<td>0.029</td>
<td>Decrease in modelled benefit</td>
</tr>
<tr>
<td>Incremental Costs</td>
<td>£2,121</td>
<td>−£534</td>
<td>Costs associated with intervention decrease rather than increase</td>
</tr>
<tr>
<td>ICER</td>
<td>£37,985 per QALY</td>
<td>−£20</td>
<td>Marked change in favour of intervention</td>
</tr>
<tr>
<td></td>
<td>Memantine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>Quantified trend towards benefit</td>
<td>Quantified trend towards benefit</td>
<td>None</td>
</tr>
<tr>
<td>Function</td>
<td>Quantified statistically significant benefit</td>
<td>Quantified statistically significant benefit</td>
<td>More confidence about presence and size of benefit</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Quantified trend towards benefit</td>
<td>Quantified statistically significant benefit</td>
<td>None</td>
</tr>
<tr>
<td>Global impact</td>
<td>Quantified statistically significant benefit</td>
<td>No empirical data</td>
<td>None</td>
</tr>
<tr>
<td>Institutionalisation</td>
<td>No empirical data</td>
<td>No empirical data</td>
<td>None</td>
</tr>
<tr>
<td>Incremental QALYs</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Unclear</td>
</tr>
<tr>
<td>Incremental Costs</td>
<td>£37–53,000 per QALY</td>
<td>£32,100 per QALY</td>
<td>Change in favour of intervention</td>
</tr>
</tbody>
</table>

BSC, best supportive care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

Statistically significant refers to results which were unlikely to be accounted for by chance, typically where 95% CI did not include values indicating no difference.
all drugs were more cost-effective compared with BSC than previously thought. In the case of all the AChEIs, the modelled QALY gains were achieved at lower cost—AChEIs dominated BSC. There was uncertainty, but as >99% of possible values in the probabilistic sensitivity analysis fell below a threshold of £30,000/QALY this was unlikely to affect a policy decision (see Supplementary data available Age and Ageing online, Figure Appendix S3). In the original HTA, the ICERs were all greater than £50,000/QALY [8]. The cost-effectiveness of memantine changed less, but again the estimate in 2010 was improved relative to the earlier estimate and much closer to the decision-making threshold of £20–30,000/QALY. Again there was uncertainty as illustrated in the probabilistic sensitivity analysis (see Supplementary data available Age and Ageing online, Figure Appendix S4). Comparing memantine to BSC 38% of values fell below a threshold of £30,000/QALY.

Separating the ICERs into changes in benefit and cost reveals that the improved cost-effectiveness for the AChEIs largely came about through a marked reduction in the modelled costs of introducing the drugs, particularly drug acquisition and the costs of full time institutionalised care. There were similar increments in mean QALYs per patient. Data were not provided in the 2004 report to allow us to separate the components of the ICER for memantine.

Discussion

The main findings of the analysis are that there have been changes in the evidence between 2004 and 2010. These particularly relate to the results of the health economic models and particularly in turn to the estimates of impact on cost. This resulted from considerable additional development of the economic model to overcome criticisms levelled at the version used in 2004. Although more subtle, improvement in the evidence base was also apparent for effectiveness, with increases in the amount of information from trials already available in 2004 leading to estimates of effect which were quantified and statistically significantly different from BSC, rather than just trends towards benefit. Both the improved confidence about the beneficial effects of the drugs and the more optimistic estimates of cost-effectiveness are consistent with the changes in NICE’s recently released guidance. The shift in conclusions that AChEIs and memantine are cost-effective is also consistent with estimates of other cost-effectiveness analyses performed since 2004 [19–23].

The approach we adopted adhered to recognised standards for both systematic reviews and health economic modelling [24–26]. The research was conducted by an experienced team, with no conflicts of interest, working to a pre-specified protocol [27] and building on previous peer reviewed research [8]. We liaised closely with the original research team and the work was closely scrutinised during the NICE technology appraisal process. We were transparent about the origin, justification and nature of the changes in the economic model. Limitations of our research include the lack of evidence on the key outcome of time to institutionalisation and our lack of access to individual patient data in the included trials. Using such data, manufacturers were able to consider the relevant population subsets of trials otherwise excluded from our analyses, because the majority of included participants in the trials in question did not meet our inclusion criteria. Meta-analyses based on such data further reinforced evidence on the clinical effectiveness of memantine in particular. Similarly lack of individual patient data also limited our approach to considering variation in effectiveness and cost-effectiveness by subgroups of different severity. Analysis by subgroup was an important feature of the original decision, as the use of AChEIs was originally restricted to those with mild AD [4]. This was less of an issue in 2010 because of the improved estimates of effectiveness and cost-effectiveness across all licensed populations. In common with the original economic model, we continued to use a cohort-based model approach, whereas other approaches, such as discrete event simulation, whereby individual patients are modelled, might be considered more appropriate. It is thus reassuring to note that published estimates based on such modelling approaches are consistent with the findings of our model in 2010 [28].

Although the comparison presented supports the view that the change in NICE’s recent guidance is wholly consistent with the evidence base between 2004 and 2010, it also highlights that important sources of uncertainty about further evolution of cost-effectiveness remain. As such uncertainty is resolved the estimated cost-effectiveness may worsen or indeed improve still further. This in turn could change decisions on the public funding of these drugs in the future. The first source of uncertainty is that the clinical importance of the small statistically significant observed changes in cognition, function and behaviour remain unconfirmed. Current estimates of time to institutionalisation and the benefits which flow from this in terms of improved quality of life and reduced cost are based almost wholly on predictions made by models. Although this is an important source of uncertainty, it is highly unlikely that this will be resolved empirically, as it would almost certainly be deemed unethical to perform an RCT to establish the effect on time to institutionalisation when individual effects on cognition, function, behaviour and global impact are relatively well established.

The second source of uncertainty is that cost impact is critical to the current view of the cost-effectiveness of drugs to ameliorate AD being acceptable. The models predict that the cost of introducing the AChEIs in particular will lead to a small net reduction because the costs of the drugs are offset by delay in patients needing expensive full time care. Although there is some empirical evidence to support such a reduction, the estimates are susceptible to bias and disputed [29, 30]. Further evidence may emerge, but as with the effect on time to institutionalisation rigorous study designs minimising confounding are unlikely to be deemed ethical. Fortunately, it is likely that the cost of
the AChEIs will fall as generic preparations emerge, increasing the likelihood that drug costs are indeed offset by savings in the large costs associated with full time care.

Third and finally the measures of cost-effectiveness, the ICERs, are based on very small differences in costs and benefits, which in turn makes the policy decisions on which they are based intrinsically more unstable. This is explained in more detail in Supplementary data available in *Age and Ageing* online, Appendix S5.

### Key points

- Although there is evidence that the drugs donepezil, galantamine, rivastigmine and memantine are effective in AD, their cost-effectiveness has been contested.
- In England and Wales their use was restricted by NICE until recently.
- There has been a change in the evidence base between 2004 and 2010 consistent with the change in NICE guidance in 2011.
- Evidence on cost-effectiveness has improved in particular but some uncertainty remains.

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### Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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