Cost-effectiveness of functional imaging tests in the diagnosis of Alzheimer disease
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of a diagnostic work-up strategy involving a functional neuroimaging examination for the assessment of Alzheimer's disease (AD) in specialised centres. The proposed strategy comprised either magnetic resonance (MR) with dynamic susceptibility (DSC) contrast-enhanced MR imaging, or single-photon emission computed tomography (SPECT). The comparator was the conventional standard examination alone.

Type of intervention
Diagnosis.

Economic study type
The study type was cost-utility analysis.

Study population
The study population consisted of patients referred to an AD centre. It was estimated that the prevalence of AD was 56%, i.e. mild or moderate.

Setting
Hospital, community or nursing home.

Dates to which data relate
The transition probabilities came mainly from a 1999 study. The probability of death in the no AD group was taken from a 1997 source. Assumptions about the efficacy of donepezil came from a study published in 1998; those of test accuracy came from 2 studies published in 1998; and those concerning quality of life (QOL) weights came from 3 studies published in 1993, 1998 and 1999. The price year was 1998.

Source of effectiveness data
The evidence for final outcomes was based on a synthesis of previously completed studies.

Link between effectiveness and cost data
The costing was undertaken partly on data from the institution, and probably on the same patient sample as that used in the effectiveness study in 1998. Costs were also taken from studies published in 1995 and 1998, although the boundaries were unclear.

Modelling
The authors developed a decision tree containing embedded 'Markov cycle trees'. The tree branched according to strategy, and at the end of each branch was a Markov cycle tree, which enabled transitions between various health states.
and health settings. Patients were classified according to their health states, i.e. no AD, mild AD, moderate AD, severe AD or dead; these were revised every six weeks. The purpose of the model was to estimate the cost-utility of the different AD diagnostic strategies. Three cohorts of 32,000 trials each were simulated for each diagnostic strategy, and the results for each strategy were averaged.

Outcomes assessed in the review
The outcomes assessed for mild and moderate AD were transition probabilities, prevalence, QOL weights and sensitivity.

The outcome assessed for computed SPECT, visual SPECT and MR imaging plus DSC MR imaging, was specificity for AD.

Study designs and other criteria for inclusion in the review
The design of the studies used in the review was not reported. The studies were chosen on the basis of relevance to the problem studied and the necessary effectiveness estimates.

Sources searched to identify primary studies
The sources searched to identify the literature were not specified.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Eight studies were included.

Methods of combining primary studies
See sensitivity analysis.

Investigation of differences between primary studies
Not reported.

Results of the review
For the base case, the sensitivity for mild AD was estimated to be 0.88 for MR imaging plus DSC MR imaging, 0.50 for visual SPECT and 0.90 for computed SPECT. The sensitivity estimates for moderate AD were 0.95, 0.74 and 0.90 for MR imaging plus DSC MR imaging, visual SPECT and computed SPECT, respectively. The specificity for mild AD was estimated to be 0.96 for MR imaging plus DSC MR imaging, 1 for visual SPECT and 0.87 for computed SPECT. The effectiveness was estimated as the risk ratio of the transition probabilities. The risk ratios were 0.5 in the base case for mild to moderate AD, and 2.36 in the base case for moderate to mild AD. Only a selection of the data are reported in this review.

Methods used to derive estimates of effectiveness
The effectiveness estimates for standard examination were derived from the authors’ assumptions, and from inferences
loosely based on evidence from the literature and experience.

**Estimates of effectiveness and key assumptions**
It was assumed that the sensitivity of standard examination was 0.75 for mild and moderate AD, and the specificity for AD was 0.90. The duration of drug treatment and effectiveness was estimated at 18 months. No further treatment was given beyond this point, and follow-up was ceased.

**Measure of benefits used in the economic analysis**
The benefits used in the economic analysis were measured in terms of Quality-Adjusted-Life-Years (QALYs) gained by using the intervention. The QALYS assigned weights for patients without AD were estimated at 0.826 on a scale of 0 (dead) to 1 (perfect health), on the basis of the mean of the time trade-off scores for men and women aged 65 to 84 years, which was derived from a study of community preferences. QALYS weights for patients with AD were based on the Health Utilities Index Mark 2. The results were simulated using the calibrated Markov model. The calibration parameters were derived from the literature. Future QALYS were discounted at 3% annually.

**Direct costs**
The costs were estimated from a societal perspective. The direct costs estimated in the study were the cost of initial consultations, follow-up visits, laboratory tests, non-enhanced CT, non-enhanced MR imaging, MR imaging plus DSC MR imaging, visual SPECT, computed SPECT, donepezil treatment, costs of mild, moderate and severe AD to the community and nursing home, cost of no AD and cost of patients’ travel. The estimation of some quantities and costs, for example laboratory test costs, was based on a detailed assessment of resource use at Massachusetts General Hospital, its patient records after 1998 and, in particular, the hospital's accounting data. The cost estimates of initial consultations, follow-up visits, non-enhanced CT, non-enhanced MR imaging, MR imaging plus DSC MR imaging, visual SPECT and computed SPECT were based on the Medicare Reimbursement Rates. The cost estimates of donepezil treatment were based on the study of Neumann et al (see Other Publications of Related Interest no.1). The costs of mild, moderate and severe AD to the community and nursing homes were estimated on the basis of Leon et al. (see Other Publications of Related Interest no.2). The costs of no AD were estimated on the basis of the US Bureau of Labor Statistics (see Other Publications of Related Interest no.3) as was the cost of patients’ travel. All costs were converted to US$ for the year 1998. Future costs were discounted at 3% annually. Quantities and costs were not analysed separately.

**Statistical analysis of costs**
Costs were not analysed statistically.

**Indirect Costs**
The indirect costs measured in the study were:
- carers’ costs estimated at the US mean wage of $12.78 per hour; and
- patient’s costs, estimated at $50 for an 8-hour trip. This was derived from the median income of persons aged at least 65 years.

Future costs were discounted at 3% annually. Costs were analysed separately. The estimation of indirect costs was based on the US Bureau of Labor Statistics (see Other Publications of Related Interest no.4).

**Currency**
US dollars ($). No conversions were reported.
Sensitivity analysis
The authors performed several one-way and one two-way sensitivity analyses. The purpose was to show the variability of the incremental cost-effectiveness ratio (ICER) with parameter variability in terms of treatment duration, disease progression, the ratio of moderate to mild disease prevalence, cost estimates and QOL weights for AD, and the use of alternative drugs for treatment of AD, given each strategy. All variations from the base case were according to the authors' assumptions, with the exception of QOL weight, for which another point estimate from the literature was given. The base case was stated to have used the "best point estimates for data inputs".

Estimated benefits used in the economic analysis
The results of the base-case analysis showed that MR imaging plus DSC MR imaging had an incremental benefit of 0.0029 QALYs versus standard examination. Visual and computed SPECT had a lower number of QALYs than the standard examination: 0.9851 and 0.9888, respectively.

Cost results
Under the base-case analysis, standard examination was the least expensive strategy at a cost of $54,762. Visual SPECT cost $55,362, computed SPECT cost $55,549 and MR imaging plus DSC imaging cost $55,769.

Synthesis of costs and benefits
As a measure of synthesis of costs and benefits, the authors used incremental cost effectiveness ratios (ICERs) to show how the incremental costs contributed to an incremental QALY for one test strategy versus another. The treat-all strategy dominated all other strategies, but was "...excluded from further analysis since (the authors) goal was to evaluate functional neuroimaging tests relative to one another and to the standard diagnostic work-up. Also treat all was not clinically relevant". Under the base-case analysis, MR imaging plus DSC imaging versus gave an ICER of $479,500 per QALY, compared with standard examination.

For the other strategies studied: visual and computed SPECT contributed to lower costs and lower QALYS, compared with the standard examination, and were therefore dominated. Visual and computed SPECT were generally dominated in all scenarios. The exceptions were those that assumed prevalence of mild to moderate AD stage at 1:1, where the computed SPECT gave an ICER of $816,700 per QALY, and for higher QOL weights for AD patients, where the ICER was 1,900,000 per QALY. The ICER for MR imaging plus DSC imaging only fell below $100,000 in 3 cases: low sensitivity (0.5) and specificity (0.8), and drug X (risk ratio 0.1 for mild to moderate AD), giving $24,680 per QALY; low sensitivity (0.5) and specificity (0.8), and drug Y (risk ratio 0.25 for mild to moderate AD), giving $72,950 per QALY; low sensitivity (0.5) and specificity (0.8), and longer duration of donepezil (48 months), giving $58,930 per QALY.

Authors' conclusions
The authors concluded that given the effectiveness of the currently available therapeutic agents, it was not cost-effective to add functional imaging to the standard diagnostic work-up for AD. The ICER of MR imaging plus DSC MR imaging was $479,500 per QALY gained, which is insufficient for funding in the US. SPECT methods, either visual or computed, were dominated in cost and effectiveness by the standard imaging examination under the base-case assumptions.

CRD COMMENTARY - Selection of comparators
A justification was provided for the comparators used, namely that they represented important, currently available diagnostic strategies of AD in the authors' setting. You, as the user of the database, should decide if these are widely used health technologies in your own setting.
Validity of estimate of measure of benefit
The authors did not state that a systematic review of the literature had been undertaken in order to obtain their effectiveness outcomes. As the authors admit, several relevant benefits were excluded from the study: reduction in uncertainty to the patient; allowance for planning care; and avoidance of the radiation exposure necessary in SPECT. Also, given the lack of probability information on parameters, a threshold analysis with various ICER thresholds would have been useful for producing a range of parameter values more directly linked to decision making.

Validity of estimate of costs
All categories of cost relevant to the perspective adopted were included in the analysis. Some costs and quantities were reported separately, although not for the largest source, i.e. the care of someone with AD. The resource use and unit costs were derived from published sources, but it was unclear when charges were used. A sensitivity analysis of costs was included, although the ranges appear to be only reimbursement rate or resource cost.

Other issues
The authors made appropriate comparisons of their findings with those from other studies, but did not generally present the results of their findings selectively. They reported a number of limitations of their study, namely the study modelled a one-time diagnostic examination, as opposed to repeated rounds of testing and a community-wide screening programme. In addition, in settings other than AD centre, sensitivity and specificity of standard examination could be expected to be lower, thus resulting in a higher cost-effectiveness of the functional imaging tests. It is interesting that treat all was the dominant strategy, and yet the authors dismissed this. Some measure of drug adverse effects may have been useful.

Implications of the study
Given the parameter estimates, it does not appear to be cost-effective to include functional imaging in the diagnostic strategy for AD. Further research is required to estimate the sensitivity of the standard examination for the diagnosis of AD. This is necessary because there is currently no standard-of-reference test for AD prior to autopsy. In addition, more data on the long-term effectiveness of AD drug therapies are required.

Source of funding
Supported by Pfizer.

Bibliographic details

PubMedID
11012424

DOI
10.1148/radiology.217.1.r00se1358

Other publications of related interest


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Alzheimer Disease /diagnosis /drug therapy /radionuclide imaging; Contrast Media; Cost-Benefit Analysis; Decision Trees; Health Care Costs; Humans; Indans /therapeutic use; Magnetic Resonance Imaging /economics; Markov Chains; Models, Economic; Nootropic Agents /therapeutic use; Piperidines /therapeutic use; Quality-Adjusted Life Years; Sensitivity and Specificity; Tomography, Emission-Computed, Single-Photon /economics

**AccessionNumber**
22000001532

**Date bibliographic record published**
31/01/2002

**Date abstract record published**
31/01/2002