Cost-effectiveness of PET in the diagnosis of Alzheimer disease
McMahon P M, Araki S S, Sandberg E A, Neumann P J, Gazelle G S

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
Fluorine-18 fluorodeoxyglucose positron emission tomography (PET), single-photon emission computed tomography (SPECT), and dynamic susceptibility-weighted contrast material-enhanced magnetic resonance imaging (DSC-MRI) were compared as functional imaging additions to the standard clinical examination, for the diagnosis of Alzheimer's disease (AD) in patients with dementia.

Type of intervention
Diagnosis and further treatment.

Economic study type
Cost-utility analysis.

Study population
The target population comprised a hypothetical cohort of community-dwelling patients with mild or moderate dementia who presented to a specialised AD centre.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The quality of life weights related to a study published in 1998. Data on the sensitivity and specificity of the diagnostic methods examined were derived from studies published between 1985 and 2001. The AD prevalence at diagnosis, the drug effects, and the transition probabilities used in the model were derived from data published from 1999 to 2000. The costs of diagnostic methods and AD medical care were based on 1999 data. They were expressed in 1999 US dollars, adjusted for inflation.

Source of effectiveness data
The effectiveness data were derived from a review of published studies. However, in the case of the test characteristics of the standard clinical examination, the data were estimated on the basis of published data and the authors’ opinion.

Modelling
A model was used to compare the different strategies in terms of their costs and benefits. It was described in detail elsewhere (see Other Publications of Related Interest). The model was based on a hypothetical cohort of community-dwelling patients with mild or moderate dementia, who presented to a specialised AD centre. Following diagnosis and treatment (if any), the patients transited between disease stages (mild, moderate, severe, not AD, death) and care settings (community, nursing home) and accrued costs and benefits for each cycle. The timeframe of the base-case analysis was 18 months. For each scenario, 100,000 Monte Carlo trials were simulated.
Outcomes assessed in the review
The outcomes assessed in the review were:

- the quality of life weights for different disease stages and care settings;
- the annual transition probabilities between disease stages and also between care settings;
- AD prevalence at diagnosis;
- treatment effects (transition risk ratio); and
- the sensitivity and specificity of all diagnostic strategies for the detection of AD.

Study designs and other criteria for inclusion in the review
Not stated.

Sources searched to identify primary studies
Not stated.

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

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

Number of primary studies included
The effectiveness data were derived from 14 studies. Approximately 8 of these were probably primary studies.

Methods of combining primary studies
The effectiveness data were not combined.

Investigation of differences between primary studies
Not reported.

Results of the review
The quality of life weights for each disease stage, expressed as the quality-adjusted life-years (QALYs), were:

- for mild AD in the community, 0.37;
- for mild AD in the nursing home, 0.52;
- for moderate AD in the community, 0.18;
- for moderate AD in the nursing home, 0.21;
- for severe AD in the community, 0.02;
for severe AD in the nursing home, 0.00; and
for not AD but other dementia, 0.80.

The annual transition probabilities between disease stages used in the model were:
for mild-to-mild AD, 0.614;
for mild-to-moderate AD, 0.322;
for mild-to-severe AD, 0.042;
for mild AD to dead, 0.021;
for moderate-to-mild AD, 0.043;
for moderate-to-moderate AD, 0.565;
for moderate-to-severe AD, 0.339;
for moderate AD to dead, 0.053;
for severe-to-mild AD, 0.000;
for severe-to-moderate AD, 0.000;
for severe-to-severe AD, 0.847;
for severe AD to dead, 0.153;
for not AD to not AD, 0.957; and
for not AD to dead, 0.043.

The community to nursing home probability was 0.038 for mild AD, 0.110 for moderate AD, and 0.259 for severe AD.

The AD prevalence at diagnosis was 0.44 for not AD, other dementia, and 1.5 to 1.0 for mild-to-moderate AD ratio.

The donepezil transition risk ratio was 0.50 for mild to moderate AD, and 2.36 for moderate to mild AD.

The sensitivity of PET for the detection of mild or moderate AD was 0.94, and the specificity was 0.72.

The sensitivity of SPECT for the detection of mild or moderate AD was 0.90, and the specificity was 0.87.

For DSC-MRI, the sensitivity was 0.88 for the detection of mild AD and 0.95 for moderate AD, and the specificity was 0.96.

For the standard clinical examination, the sensitivity was 0.70 for the detection of mild AD and 0.80 for moderate AD, and the specificity was 0.73.

Methods used to derive estimates of effectiveness
The authors made assumptions to derive some of the model parameters.

Estimates of effectiveness and key assumptions
The authors estimated the sensitivity of the standard examination for the detection of mild or moderate AD, on the
basis of results derived from four studies. The authors also assumed that the use of donepezil in patients with non-AD-related dementia would lead, in the baseline analysis, to neither benefits nor side effects. Moreover, it was assumed that non-AD-related dementia was reversible, and that patients with this condition had a quality of life equivalent to that of age-matched individuals with normal brain function. This assumption was in agreement with the results of another study.

Measure of benefits used in the economic analysis
The benefits were expressed as the gains in QALYs. Health-related quality of life weights were based on the Mark III version of the Health Utilities Index (HUI3). The HUI3 weights for patients with AD were derived from existing data that were stratified by care setting (community or nursing home) for the model. The HUI3 weights for age-matched community-dwelling Canadians were derived from the literature and used for patients without AD.

Direct costs
The direct costs measured were consistent with the societal perspective adopted by the authors. These included the costs of the methods examined (PET, SPECT, DSC-MRI, standard examination, donepezil treatment) and follow-up visits, annual costs of AD care for combinations of different stages (mild, moderate, severe AD, non-AD dementia) and health care settings (community, nursing home), and travel costs. The standard examination costs were further analysed in terms of the consultation costs, laboratory costs, and non-enhanced CT costs. The resources were not reported separately from the prices.

The cost data for SPECT and DSC-MRI were based on 1999 Medicare reimbursements for CPT codes, adding the costs for computerised data manipulation. Medicare reimbursements for CPT codes included professional and technical components, which were derived from the CodeManager software. The same source was used to extract the costs of consultations and non-enhanced CT used in the standard examination. For PET, a 1999 resource use estimate was adopted, determined by cost-accounting software. The laboratory tests provided in the standard examination were also based on resource use estimates. The annual costs of AD care were derived using a study published in 1999. It was unclear how the travel expenses were estimated. All the costs were expressed in 1999 US dollars, adjusted for inflation using the medical care component of the consumer price index. The future costs were discounted at an annual rate of 3%. Discounting was appropriate since the timeframe of the study was 18 months.

Statistical analysis of costs
The total costs of each comparator were presented as mean values, along with standard deviations (SD) and standard errors (SE) (these were probably adjusted values, based on the cost data for AD care, adopted from another study).

Indirect Costs
Patient and caretaker opportunity costs were included. They were derived from the "Consumer expenditure survey" of 1999, using an estimate of 2,080 working hours per year (8 hours per day) and the average annual income before tax. The indirect costs were also expressed in 1999 US dollars, adjusted for inflation using the medical care component of the consumer price index. They were discounted at an annual rate of 3%.

Currency
US dollars ($).

Sensitivity analysis
A one-way sensitivity analysis was carried out. The key variables examined were:

- the specificity of PET,
- the effectiveness of therapy (two hypothetical drugs with different effectiveness from that of donepezil were assumed
for this purpose,

the duration of effectiveness,

the side effects of therapy when false-positive cases were treated,

the quality of life weights (HUI3 was replaced by HUI2 which has significantly higher weights for the same condition),

the costs of diagnostic methods (varying by +/- 50%),

the indirect costs, and

the test characteristics of the standard clinical examination (more lenient standard examination was assumed).

A further scenario modelled was the treatment of patients who had positive results for either examination (PET or standard examination). The ranges for the key variables were selected on the basis of published data that differed significantly from that used in the base-case analysis. A threshold analysis was also provided for the cost of the perfect examination, below which this examination would yield cost-savings.

**Estimated benefits used in the economic analysis**

The QALYs gained per patient (presented as mean values +/- SD) were:

- 0.7092 (+/- 0.4120) (SE=0.001303) with the standard examination,
- 0.7109 (+/- 0.4110) (SE=0.001300) with DSC-MRI,
- 0.7063 (+/- 0.4127) (SE=0.001305) with PET,
- 0.7093 (+/- 0.4137) (SE=0.001308) with SPECT,
- 0.7138 (+/- 0.4085) (SE=0.001292) with perfect examination, and
- 0.7126 (+/- 0.4083) (SE=0.001291) with treat all dementia.

PET and SPECT showed the same benefits with the standard clinical examination. DSC-MRI had an additional benefit of 0.0017 QALYs per patient. Perfect examination led to an incremental benefit of 0.0046 QALYs per patient, compared with the standard clinical examination, whereas the option of "treat all dementia" resulted in an additional 0.0034 QALYs per patient. These benefits were calculated for a timeframe of 18 months. The QALYs were discounted at an annual rate of 3%.

**Cost results**

The mean costs per patient were:

- for standard examination, $56,859 (+/- 18,569) (SE=58.72);
- for DSC-MRI, $57,877 (+/- 18,927) (SE=59.85);
- for PET, $58,590 (+/- 18,799) (SE=59.45);
- for SPECT, $58,872 (+/- 18,736) (SE=59.25);
- for perfect examination, $57,876 (+/- 18,907) (SE=59.79); and
- for treat all dementia, $57,339 (+/- 18,009) (SE=56.95).
Using the standard examination as the baseline, the incremental costs of the interventions examined were $1,018 for DSC-MRI, $1,017 for perfect examination and $322 for treat all dementia. The incremental costs were not reported for PET or SPECT, as standard examination dominated the analysis (was both cheaper and more effective). The costs were calculated for a timeframe of 18 months. The future costs were discounted at 3%.

**Synthesis of costs and benefits**

The incremental cost-effectiveness ratios (ICERs) resulted from the combination of the estimated costs and benefits of each intervention. All of the interventions were compared with standard clinical examination.

PET and SPECT were dominated by standard examination (standard examination was both cheaper and more effective).

Compared with the standard examination, the ICER was $598,800/QALY gained for DSC-MRI, $221,100/QALY gained for perfect examination and $141,200/QALY gained for the "treat all dementia" option.

DSC-MRI dominated SPECT, while "treat all dementia", and "perfect examination" dominated all functional imaging strategies considered.

The sensitivity analysis showed that the parameters examined specifically influenced the ICER of DSC-MRI. This was decreased with improved drug effectiveness ($81,700 - 119,400/QALY), or with 48 months' duration of effectiveness ($122,800), but it was increased dramatically with 6 months' duration of effectiveness ($1,9 million). The inclusion of adverse effects in non-AD demented patients treated with donepezil resulted in an ICER of $74,400/QALY for DSC-MRI. The ICERs of PET and SPECT were generally robust. The exception was when PET was performed in patients with negative standard examination (treatment if either PET or standard examination results were positive), in which case the overall effectiveness of PET was increased. Variables such as diagnostic and opportunity costs, quality of life weights, and test characteristics did not change the results significantly.

**Authors' conclusions**

Dynamic susceptibility-weighted contrast material-enhanced magnetic resonance imaging (DSC-MRI), added to the standard examination, may be preferable to positron emission tomography (PET) for the diagnosis of Alzheimer's diseases (AD). However, it still carries a high incremental cost-effectiveness ratio (ICER) in comparison with the standard examination alone. Improvements in therapies and non-pharmacologic strategies for AD treatment would result in a more favourable ICER for functional imaging strategies.

**CRD COMMENTARY - Selection of comparators**

The authors chose to compare PET and other functional neuroimaging examinations (SPECT, DSC-MRI) as additional strategies to the standard examination used to detect AD, in patients with mild or moderate dementia. The choice of PET was justified since it is an effective method. However, it is subject to high costs, it is not reimbursed by Medicare as a diagnostic method of AD, and there is no clear evidence of improved clinical outcomes after the diagnosis of AD. The other two neuroimaging examinations were probably selected as effective, although costly, additional strategies to the standard examination. The options of "perfect examination" and "treat all dementia" were not clearly justified. The reader must decide whether the standard examination described, used as the baseline comparator, is similar to that used in your own setting for the diagnosis of AD in patients with mild or moderate dementia.

**Validity of estimate of measure of effectiveness**

It was not stated that the effectiveness data were extracted from a systematic review. The authors used data from earlier studies without justifying their choice. However, in cases where the data were insufficient or controversial, the authors made reasonable assumptions, or addressed the controversial issues and variability in the data through the sensitivity analysis.
Validity of estimate of measure of benefit
The estimation of benefits was modelled. The model used was appropriate, as it considered the test characteristics (sensitivity and specificity) of the diagnostic methods examined, the consequent treatment effects, and transition probabilities for all different health stages and care settings involved after the diagnosis of AD.

Validity of estimate of costs
The perspective of the study was stated to have been societal. All the categories of costs relevant to this perspective seem to have been examined in the study, although it was unclear what the "AD care" costs for different stages of AD and care settings included. Moreover, these costs were adopted from another study and it was not reported on what basis they were estimated. There was no separate analysis of different resources and unit costs used in the economic evaluation. The prices of diagnostic methods were based on Medicare reimbursements, which would not reflect opportunity costs. The costs were discounted at an annual rate of 3%. They were presented as mean values, along with SDs and SEs, possibly derived from another study used to provide the costs of AD care. A sensitivity analysis on diagnostic costs was undertaken, although the range of values used was not justified. The price year was reported.

Other issues
The authors compared their results with the results of other studies, and found them to be consistent. The issue of the generalisability of the results to other settings was not addressed. The study examined the impact of diagnostic methods on the quality of life of patients with mild or moderate dementia only. Patients with severe dementia were excluded from the model, because donepezil was not indicated for severe AD and neuroimaging would not be necessary to confirm the diagnosis.

One limitation of the study, according to the authors, was that it assumed that the results from standard examination and PET were independent, which is not the case. Inclusion of the positive correlation between examination results would probably result in PET being even less effective overall. Moreover, the analysis did not address the primary care or community-based screening examinations in asymptomatic individuals with AD, although there was evidence that neuroimaging could contribute to the identification of patients at high risk of developing the disease. The authors appear to have fully reported the results and their conclusions reflected the scope of the analysis.

Implications of the study
The authors emphasised the value of an accurate neuroimaging examination for patients with inconclusive standard examination results. Besides enabling the initiation of therapy, an earlier diagnosis of AD would eliminate uncertainty and allow time to plan for caretaking, legal and financial arrangements for the patient. These issues, although important, are difficult to include in QALY measures.

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Other publications of related interest


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