The value of the managed entry of new drugs: a case study of donepezil
Payne K, Davies L M, Noyce P R, Weiss M C

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
Three models to manage the entry of new drugs (in the case, donepezil) into practice were examined.

In model 1, the Health Authority managed the entry of donepezil by using existing services with consultant assessment and general practitioners (GPs) taking up prescribing after 5 weeks.

In model 2, the Health Authority managed the entry of donepezil by using existing services with consultant-only prescribing.

In model 3, the Health Authority managed the entry of donepezil by establishing a specialist service with consultant-only prescribing.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with mild to moderate Alzheimer's disease.

Setting
The setting was primary and secondary care. The economic analysis was conducted in Manchester, UK.

Dates to which data relate
The effectiveness data were collected from existing sources published between 1995 and 2000. The resource data were obtained from various sources published between 1991 and 1997. The price year was 1997.

Source of effectiveness data
The effectiveness data were derived from a review of completed studies, augmented by authors' assumptions.

Modelling
A decision analysis and simulation were used to explore how the models differed in terms of their costs and effectiveness. The time horizon for the managed entry process varied between the health authorities, depending on the speed of the decision-making process. The time horizon for the cost assessment was 12 months.

Outcomes assessed in the review
The outcomes assessed in the review and used as model inputs were:

- the probability that managed entry was effective;
- the probabilities of being prescribed donepezil with or without managed entry; and
- the appropriateness of prescribing donepezil with and without managed entry.

The value changes in health (utilities) were also assessed.

**Study designs and other criteria for inclusion in the review**

The probability that managed entry was effective was estimated from a national survey of 211 pharmacists in health authorities and NHS trusts. The probability of being prescribed donepezil with managed entry was calculated from the actual uptake rate of donepezil into practice for each study site, the proportion of patients who would require treatment, and published prevalence data. The probability of being prescribed donepezil with no managed entry was based on the national rate of donepezil use. The appropriateness of prescribing donepezil with managed entry was estimated using site-specific data. The appropriateness of prescribing donepezil with no managed entry was estimated from a published systematic review of the appropriateness of prescribing, published in 1996. The utility values were derived from published utility data from 679 caregivers of patients with Alzheimer's disease using the Health Utilities Index Mark 2 (HUI2) and mark 3 (HUI3).

**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**

Not stated clearly.

**Methods of combining primary studies**

Not stated.

**Investigation of differences between primary studies**

Not stated.

**Results of the review**

The probability that managed entry was effective was 0.46 in all sites.

The probability of prescribed donepezil given managed entry effective was 0.02 in site 001, 0.04 in site 007 and 0.06 in site 010.

The probability of prescribed donepezil given managed entry not effective was 0.18 in all sites.

The probability of prescribed donepezil with no managed entry was 0.18 in all sites.
The probability of donepezil prescribed (or not prescribed) appropriately given managed entry effective was 0.69 in site 001, 0.61 in site 007 and 0.68 in site 010.

The probability of donepezil prescribed (or not prescribed) appropriately given managed entry not effective was 0.34 in all sites.

The probability of donepezil prescribed (or not prescribed) appropriately given no managed entry was 0.34 in all sites.

The utility value of donepezil prescribed (or not prescribed) appropriately was 0.39 (standard deviation, SD=0.24) with HUI3 and 0.69 (SD=0.16) with HUI2.

The utility value of donepezil prescribed (or not prescribed) inappropriately was 0.19 (SD=0.20) with HUI3 and 0.53 (SD=0.17) with HUI2.

Methods used to derive estimates of effectiveness
On the basis of a meta-analysis of 3 trials, the clinical effectiveness was estimated to be an improvement of -2.61 (95% confidence interval, CI: -3.45 - -1.79) points on the ADA-Cog scale (70-point scale). This was converted to a percentage value.

Estimates of effectiveness and key assumptions
For an average dose of 5 mg per person per day, the outcome was a 3.7% (95% CI: 2.6 - 4.9) improvement for the patient population when donepezil was appropriately prescribed. If donepezil was prescribed inappropriately, or was appropriately not prescribed, the outcome was assumed to be status quo with no change in the ADAS-Cog score. The minimum decline of 6 ADAS-Cog scale points was used as a conservative estimate for the main analysis.

Measure of benefits used in the economic analysis
The health benefits were measured in terms of cognitive function gained (%), the number of patients with a clinically important change in cognitive function, and the number of quality-adjusted life-years (QALYs) gained.

Direct costs
The perspective of the NWHR health authorities and NHS trusts was adopted. Four components of resource use were evaluated:

resource use associated with the decision-making process of managed entry, including the individual's time and travel costs, but excluding the cost of follow-up reviews and assessments of patients at clinics;

resource use associated with the quantity of donepezil prescribed;

resource use associated with formal health and social care for Alzheimer's disease; and

the number of inpatient beds required by patients with Alzheimer's disease.

The prescribing costs associated with a maximum of 1 year of treatment with donepezil were included. Resource use was identified from the minutes of APC meetings, on-file letters of correspondence relating to the introduction of donepezil into practice, and face-to-face interviews. The quantity and cost of donepezil prescribed were estimated from Prescribing Analysis and Cost (PACT) data and NHS trust pharmacy department data for the year 1997 to 1998. The cost of formal health and social care for Alzheimer's disease was estimated from published estimates for dementia. It was combined with published prevalence data to estimate the costs of mild to moderate Alzheimer's disease for each population profile. All the costs were standardised to a base year, 1997.

Statistical analysis of costs
No statistical analysis of the costs was carried out.

**Indirect Costs**
No indirect costs were included in the analysis.

**Currency**
UK pounds sterling (¥).

**Sensitivity analysis**
One-way sensitivity analyses were performed using a predefined protocol, which is available from the authors on request.

**Estimated benefits used in the economic analysis**
The side effects of treatment were assumed to be negligible and were not considered in the economic analysis.

The baseline expected effectiveness (% improvement of cognitive function) with managed entry was -3.57% in site 001, -3.83% in site 007 and -3.51% in site 010.

The baseline expected effectiveness with no managed entry was -4.43% in each site.

The mean net expected effectiveness was 0.847% (95% CI: 0.816 - 0.878) in site 001, 0.584% (95% CI: 0.557 - 0.610) in site 007 and 0.947% (95% CI: 0.917 - 0.976) in site 010.

The baseline expected QALYs with managed entry was 0.290 in site 001, 0.283 in site 007 and 0.289 in site 010.

The baseline expected QALYs with no managed entry was 0.258 in each site.

The mean net expected outcome was 0.03 (95% CI: 0.023 - 0.041) in site 001, 0.03 (95% CI: 0.017 - 0.033) in site 007 and 0.03 (95% CI: 0.024 - 0.041) in site 010.

**Cost results**
The baseline expected cost of managed entry was 2,770,000 in site 001, 2,645,000 in site 007 and 6,690,000 in site 010.

The baseline expected cost of no managed entry was 2,755,000 in site 001, 2,632,000 in site 007 and 6,664,000 in site 010.

The mean net cost (difference between managed and no managed entry) was 14,927 (95% CI: 14,365 - 15,489) in site 001, 12,431 (95% CI: 11,901 - 12,961) in site 007 and 25,282 (95% CI: 23,980 - 26,584) in site 010.

**Synthesis of costs and benefits**
The expected cost per unit of cognitive function gained was 18,000 for study site 001, 22,000 for study site 007 and 28,000 for study site 010.

The expected cost per person with clinically significant improvement (assuming that a 5.7% change in ADA-Cog scale is clinically significant) was between 140,000 and 230,000.

The incremental cost per QALY gained was 470,000 in site 001, 520,000 in site 007 and 8,070,000 in site 010.

The expected cost per QALY ranged from 470,000 to 19.3 million according to the HUI index used (HUI2 or HUI3) and the delay in disease progression (6 or 12 months).
Authors' conclusions
Managed entry does not appear to be a worthwhile mechanism for introducing drugs into practice. The process of managed entry of donepezil was associated with higher expected outcomes, but also with higher expected costs, compared with no managed entry.

CRD COMMENTARY - Selection of comparators
The choice of the comparators was clear. Since no standard approach to managed entry was available, it was necessary to identify a variety of specific examples. You should consider whether these are widely used health technologies in your own setting.

Validity of estimate of measure of effectiveness
The measure of effectiveness was clear, using the ADA-Cog scale. However, the authors acknowledged that this measure did not really incorporate the clinical efficacy of donepezil. According to the authors, the actual influence of managed entry on the effectiveness of donepezil in practice could not be established because accurate information on the patient outcomes of managed entry was not readily accessible. The prevalence data on mild to moderate Alzheimer's disease and the population eligible for donepezil were not of good quality (as the authors noted). The concept of appropriateness was also a potential source of uncertainty (different perceptions exist). Those features may hinder the reproducibility of the results to other settings.

Validity of estimate of measure of benefit
The authors used proxy valuations of utility (from caregivers), which may be lower than the patients' values. Thus, the analysis may have underestimated the value of improvements in the patients' health. The authors noted the limitation of using proxy utility valuations.

Validity of estimate of costs
The cost calculations were based on the only published estimate on the effect of donepezil on institutionalised care, which was not a randomised controlled trial of the drug, as the authors reported. Consequently, there was uncertainty attached to the effectiveness value of donepezil in reducing institutional care. Discounting at an appropriate rate was conducted when necessary. In addition, the price year was reported, which will aid any future reflation exercise. However, the unit costs and the quantities were not reported separately.

Other issues
The limited generalisability of the results was addressed. The authors made no comparisons of their findings with those from other studies dealing with the same topic. The authors clearly highlighted the limitations of their study. They do not appear to have reported the results selectively.

Implications of the study
The authors acknowledged that the lack of data presents serious obstacles for both researchers and policy makers wishing to develop evidence-based policy and practice. In addition, to improve managed entry and associated production of clinical guidelines, decision-makers must establish systems to monitor the impact of their drug policies.

Source of funding
Supported jointly by the Medical Research Council and the Research and Development Department of the North West Region in the form of a Special Training Fellowship in Health Services Research.

Bibliographic details

PubMedID
12701944

Indexing Status
Subject indexing assigned by NLM

MeSH
Alzheimer Disease /drug therapy; Cholinesterase Inhibitors /administration & dosage /economics /therapeutic use; Cost-Benefit Analysis; Decision Making; Drug Approval; Drug Evaluation /economics; Drug Prescriptions /economics; Drugs, Investigational /administration & dosage /economics /therapeutic use; Great Britain; Health Care Rationing /economics; Humans; Indans /administration & dosage /economics /therapeutic use; Organizational Case Studies; Piperidines /administration & dosage /economics /therapeutic use; Public Health Administration; State Medicine

AccessionNumber
22003008068

Date bibliographic record published
30/04/2004

Date abstract record published
30/04/2004