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THE VALUE OF THE MANAGED ENTRY OF NEW DRUGS

A Case Study of Donepezil

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Abstract

Objective: A United Kingdom Department of Health directive (EL[94]72) asked Health Authorities to manage the entry of new drugs into practice. There seem to be costs associated with the decision-making process of managed entry, but no clear evidence of benefit to patient populations. The objective of this study was to assess the potential costs and outcomes of different models of managed entry, using the example of donepezil in the North West Health Region of the U.K. National Health Service. This is a preliminary study designed to identify the key pieces of information required to evaluate the value of managed entry.
Methods: Decision analytic models of three Health Authorities' approaches to manage the entry of donepezil were used to estimate the expected costs and effectiveness of the process. Resource use data were obtained from published sources and the relevant Health Authority. Probabilistic sensitivity analysis was used to determine the robustness of the results.
Results: The process of managed entry of donepezil was associated with higher expected costs and higher expected outcome than no managed entry. The 95% confidence intervals for the net expected costs and net expected outcomes were relatively narrow and did not cross zero, which suggests a statistical difference between managed entry and no managed entry for donepezil. The incremental cost-effectiveness ratios for managed entry of donepezil indicate that, compared with no managed entry, there were substantial differences between the different models used in the three study sites. The expected cost per unit of cognitive function gained was between £18,000 in study site 001 to £28,000 in study site 010. The expected cost per person with a clinically significant improvement was between £140,000 and £230,000. The expected cost per QALY ranged from £470,000 to £19.3 million.
Conclusions: Managed entry does not appear to be a worthwhile mechanism to introduce drugs into practice. However, poor accessibility and availability of data means that the results are highly uncertain. The lack of data presents serious obstacles for both researchers and policy makers wishing to develop evidence-based policy and practice.

Keywords: Economics, Pharmaceutical, Cost-effectiveness analysis, Alzheimer disease, Cholinesterase inhibitors

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The high cost of drugs newly launched onto the prescription drug market has prompted decision makers to implement explicit methods of rationing supply and managing demand for their use. These include the use of local formularies and guidelines to inform healthcare decision makers and attempt to control the diffusion of new products into existing markets (8;17). In 1994, the Department of Health (England) issued the directive (EL[94]72) that asked Health Authorities to develop and agree on strategies for improving cost-effective prescribing across the primary-secondary care interface (24). The policy was a landmark document for decision makers involved with the introduction of drugs into practice. It introduced two key concepts: a) to agree and develop systems to address the cost-effectiveness of prescribing across the primary-secondary care interface; and b) to manage the entry of drugs into practice.

Subsequent to EL(94)72, Health Authorities and their nearby NHS Trusts, under guidance from the then National Health Service (NHS) Executive, were expected to plan the introduction of new drugs and manage their entry into practice. At this local level, two different types of committees assess drugs. These are Drug and Therapeutics Committees (D&TCs) and Area Prescribing Committees (APCs). D&TCs have an established tradition as a decision-making body in the NHS (19). D&TCs mainly include members of NHS Hospital Trust staff, and their main role is to "encourage rational and cost-effective prescribing in hospitals" (10;19). APCs are a relatively new concept. They are based and coordinated by Health Authorities and have representatives from local hospitals and primary care (34). Generally, APCs focus on evaluation of primary care and interface drugs that cross the boundary between hospital and general practice, whereas D&TCs assess drugs used primarily by hospital-based clinicians. There is, however, overlap and often joint representation on both committees.

The definition of *managed entry* and the operationalization of the concept were not made explicit by the executive guidance. In theory, managed entry should involve the evaluation of a drug before it has been licensed for use by the Medicines Control Agency. The evaluation should be guided by pre defined criteria and informed by good quality clinical and cost-effectiveness data. The process of managed entry should identify the target patient population for the drug and the most appropriate group of prescribers in terms of their ability to make informed prescribing decisions. The requirement for guidelines, specific funding arrangements and additional healthcare services, such as clinics, should be assessed. These systems should then be set up if considered necessary. Arrangements should be made to monitor the use of the drug in practice in terms of the relevant clinical outcome and the diffusion of the drug into practice. Following a predefined period, the drug should be reassessed using the information gathered during the monitoring process. The future use of the drug should then be reappraised.

A survey of managed entry found that decision makers took different approaches to implement the concept (27). To date, there has been no formal assessment or description of the process of managed entry, in particular, and how it relates to the introduction of drugs in general. The benefits and costs of managed entry, or planning the introduction of drugs, have yet to be evaluated. Rous et al. (30) reported their experience of managing the entry of interferon beta-1b for the treatment of relapsing/remitting multiple sclerosis. This report implied that managing the entry of a new drug was a costly exercise. It identified a clear need to divert large quantities of resources, in terms of staff and time to collate and discuss the available evidence on the potential use of interferon beta. The time Health Authority staff took to evaluate the drug meant they were not able to do other tasks. The study clearly indicated the perception that there were costs associated with the decision-making process of managed entry, but no clear evidence of benefit to the patient population who will receive the drug in practice. This suggests that there is a need for research to explore the costs and benefits of the process of managed entry. A comparative study of specific examples of managed entry

provides information on the potential economic impact of methods chosen to introduce a drug into practice. The framework for an economic evaluation of managed entry can be structured using a model that assimilates retrospective data from existing sources or a prospective study, such as a randomized controlled trial (RCT). A prospective study with direct observation of the phenomenon was not feasible at the time this modeling study was conducted. There was no information to design a prospective economic evaluation, which could deal with practical difficulties with randomization, sampling, and follow-up, representing examples of managed entry. It was necessary to structure a study using retrospective data from existing sources. The results of the economic model reported here could be used to identify the key parameters associated with the healthcare intervention and its relevant alternatives to inform the design of a prospective economic study. This is a preliminary study designed to identify the key pieces of information required to evaluate the value of managed entry.

The objective of this study was to assess the expected costs and outcomes of three models of managed entry. A survey explored the following statements about managed entry (27):

1. It is resource-intensive;
2. It effectively influences prescribing practice for new drugs;
3. It minimizes the costs of treatment by reducing inappropriate prescribing and increasing appropriate prescribing; and
4. It increases health gain by reducing inappropriate prescribing and increasing appropriate prescribing.

The survey clearly identified three models of managed entry. Decision analysis and simulation were used to explore the extent to which these models differed in terms of costs and effectiveness.

METHODS

Comparators

There is no standard approach to managed entry, and so it was necessary to identify specific examples of managed entry for evaluation (27). A telephone survey was conducted of decision makers responsible for the evaluation of drugs in NHS Trusts (chief pharmacists, $n = 17$) or Health Authorities (pharmaceutical advisers, $n = 12$) in the North West Health Region (NWHR) of the U.K. NHS. The survey was designed to identify: a) which drugs were managed into practice; b) the process used to manage entry; and c) appropriate study sites for the economic evaluation.

The survey identified donepezil as a drug that was extensively managed into practice in NWHR in 1997 (83% of Health Authority and 65% of NHS Trust respondents). The operational concepts underlying the managed entry of donepezil varied substantially between sites and respondents. From the survey, three clear models of managed entry, represented by three Health Authorities selected as study sites (study site 001, 007, and 010), were identified for donepezil (Table 1), and each described a different approach to introducing the drug into local practice. These were selected as the comparators for this modeling study.

The study sites were chosen on the following criteria: a) willingness to participate (93% of interviewees); b) availability of local data to quantify the economic process and outcome measures; and c) diversity of models of managed entry.

Perspective and Time Frame of Analysis

The economic evaluation used the viewpoint of NWHR Health Authorities and NHS Trusts involved in the managed entry of donepezil. The costs and outcomes relating to patients and

Table 1. Health Authorities, NHS Trusts, and Models of Managed Entry for Donepezil

Health Authority	NHS Trust	Model of managed entry
001	NHS Trust 001a NHS Trust 001b	*Managed entry model 1*: Health Authority managed the entry of donepezil by using existing services with consultant assessment and general practitioners taking up prescribing after 5 weeks. Date of 1st meeting: April: 1997; date of last meeting: December 1997
007	NHS Trust 007a NHS Trust 007b NHS Trust 007c	*Managed entry model 2*: Health authority managed the entry of donepezil using existing services with consultant-only prescribing. Date of 1st meeting: March 1997; date of last meeting: February 1998
010	NHS Trust 010a NHS Trust 010b NHS Trust 010c	*Managed entry model 3*: Health Authority managed the entry of donepezil by establishing a specialist service with consultant-only prescribing. Date of 1st meeting: February 1997; date of last meeting: April 1998

their carers were not included in this preliminary study. The sample was defined to represent decision makers involved in the managed entry of donepezil and the respective patients, under the care of the relevant Health Authorities, who had received this drug. The time horizon for the managed entry process varied between the Health Authorities, depending on the speed of the decision-making process (Table 1). The time horizon for the assessment of the costs of managed entry included costs for 12 months of formal health and social care associated with the introduction of donepezil.

Analytic Approach

The evaluation used cost-effectiveness analysis to compare different methods of managed entry with no managed entry for donepezil. The framework of decision analysis was used to develop a model to estimate the expected costs and expected patient outcomes of managed entry. The modeling approach was chosen to synthesize available data and information from a number of sources. Lack of previous evaluation and assessment of managed entry meant that there was insufficient information to design a robust prospective economic evaluation.

Sensitivity Analysis

Probabilistic sensitivity analysis was used to quantify the uncertainty associated with the deterministic probability estimates used to calculate the expected costs, outcomes, and incremental cost-effectiveness of managed entry. This was to test the assumption that managed entry influences the probability of events included in the total expected costs and outcomes. This implies that managed entry has little or no impact on the costs and outcomes of these component events. A predefined protocol was used to guide the sensitivity analysis (available on request) (3;4). No prior information was available to inform the choice of distribution. For this reason, the standard triangular distribution was used for all the probability variables in the model (minimum, mid, and maximum value) (7). The mid-value of the triangular distribution was assigned as the baseline value for each probability. Confidence intervals (95%) were calculated for the mean net expected costs and outcomes (where n = number of iterations).

Decision Tree Model

The same model structure was used to represent the process of managed entry. Each Health Authority's approach to managed entry was compared with the non managed entry option. Figure 1 illustrates the model structure. The non-managed entry option was defined in terms of the usual approach to introduce a drug into practice in the U.K. In the absence of managed entry, a Health Authority would simply fund any drug with a product license that was prescribed on a valid prescription. The model starts with a decision on whether or not to manage the entry of a specific drug, in this case, donepezil. Table 2 summarizes the sequence of events following the initial decision.

DATA

Estimating Probabilities

The probability that managed entry was effective, in terms of the successful implementation of the policy in the Health Authority, was estimated from a survey of decision-makers about managed entry (27). This was a national survey of 211 pharmacists based in Health Authorities and NHS Trusts that aimed to establish their views on the concept and perceived success of managed entry as a policy designed to control the introduction of drugs into practice. The results of this survey indicated that some respondents felt managed entry as a policy was effective, but some felt it was unsuccessful or were not completely sure about its effectiveness. The probability of effective managed entry was estimated as the proportion of respondents that felt the national drug policy, managed entry, was a success. The value of the probability that managed entry was effective was tested in the sensitivity analysis.

The probability of being prescribed donepezil with managed entry was calculated from: a) the actual uptake rate of donepezil into practice for each study site; b) the proportion of patients who would require treatment with the drug in each Health Authority; and c) published prevalence data.

The probability of being prescribed donepezil with no managed entry for all three study sites was based on the national rate of donepezil use. This was estimated from national prescribing data in the IMS database, which contains the total cost of donepezil sales for hospital and community in the United Kingdom (15). The national rate of donepezil use was estimated as the actual number of patients prescribed donepezil in the United Kingdom, from IMS data, divided by the expected number of patients in the United Kingdom who should be prescribed donepezil according to the prevalence of mild to moderate Alzheimer's disease, from published prevalence and national demographic data (9;20;28). The number of patients actually prescribed donepezil in the United Kingdom per year was calculated from the annual total cost of donepezil divided by the cost of a 5-mg dose of donepezil. Each patient was assumed to receive 5 mg of donepezil for 28 days per month.

The appropriateness of prescribing donepezil with managed entry and local guidelines in place was estimated using site-specific data. *Appropriate* was defined in respect to the indication for the drug and whether a patient was initiated on donepezil according to the guidelines produced and agreed on by each Health Authority. All three sites produced guidelines to advise which patients were eligible for donepezil according to diagnostic criteria. The quality of these guidelines, in terms of evaluation and classification of the level of evidence, was not assessed (12). The number of patients who were appropriately prescribed donepezil according to these site-specific guidelines was recorded. The proportion of patients in each study site who were appropriately prescribed donepezil was estimated from the number of patients appropriately prescribed donepezil divided by the estimated number of eligible patients per study site. The number of eligible patients was estimated from the prevalence of mild to moderate Alzheimer's disease and site-specific demographic data (9;20;28).

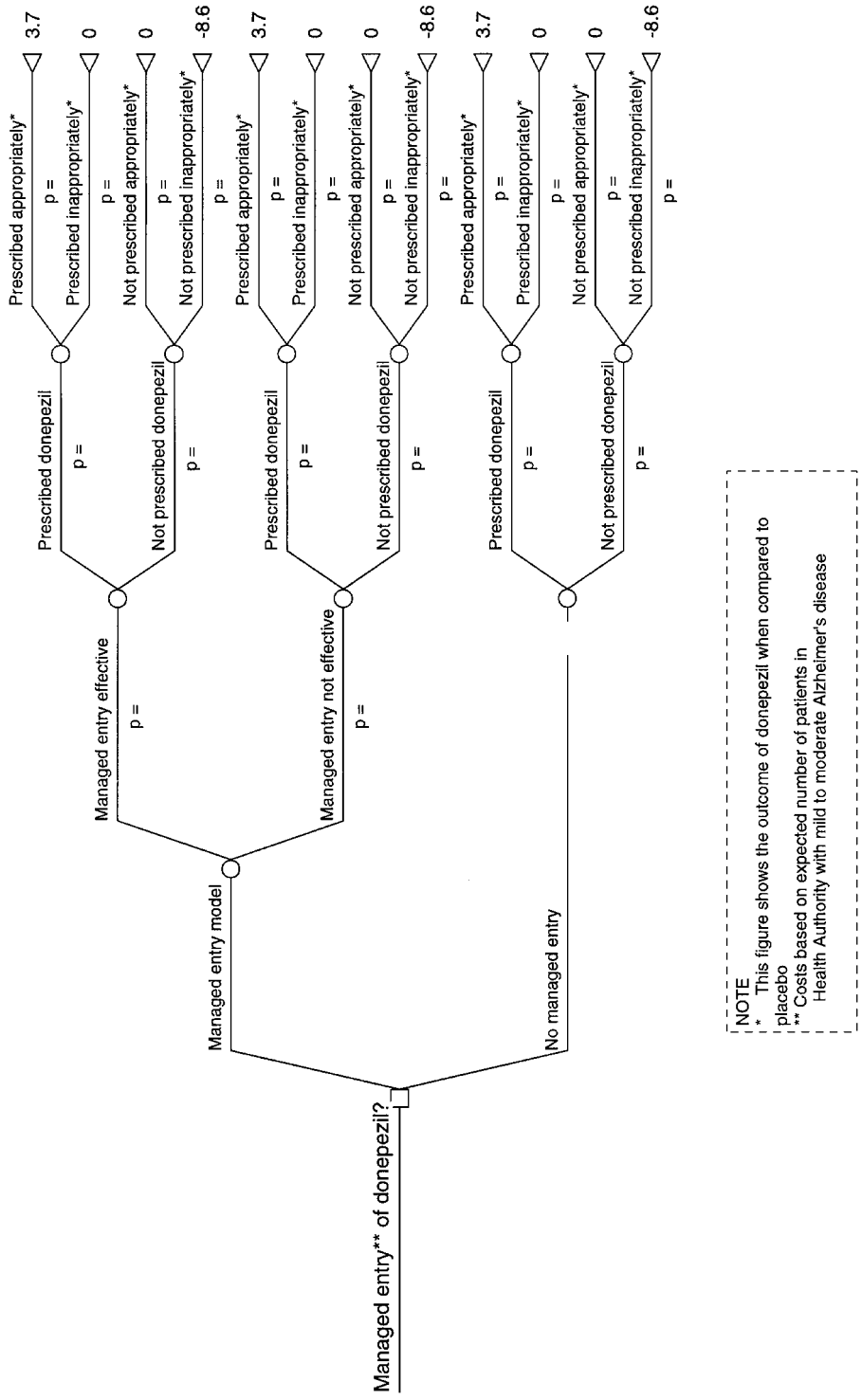

Figure 1. Decision tree for the managed entry of donepezil.

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Table 2. Description of Uncertain Events Illustrated in Figure 1

Decision	Uncertain event	Description
Manage entry of donepezil	Managed entry is [in]effective	This referred to the effectiveness of the implementation of Health Authority policies to introduce drugs into practice. It was assumed that the Health Authority geography does not affect the implementation of managed entry as a policy.
Manage entry of donepezil	Patients are [not] prescribed donepezil	This referred to whether patients with mild to moderate Alzheimer's disease are initiated on donepezil. It was assumed that managed entry will affect the probability of a patient being prescribed the respective drugs.
Manage entry of donepezil	Donepezil prescribed [in]appropriately	For the purpose of this economic evaluation, appropriate was defined in respect of the indication for the donepezil and whether a patient was initiated on it according to the guidelines produced and approved by each Health Authority or NHS Trust.
Do not manage entry of donepezil	Patients are [not] prescribed donepezil	This referred to whether patients were initiated on the selected drugs with no drug policies in place. It was assumed that national prescribing data for each drug represent the normal uptake of donepezil because there were, at the time of the study, no accepted and routinely used national guidelines in terms of managed entry.
Do not manage entry of donepezil	Donepezil is prescribed [in]appropriately	This referred to the prevalence of appropriate prescribing with no effective and specific local prescribing guidelines. The definition of appropriate was consistent with that used when a managed entry policy was in place in that it referred to whether the drug was prescribed according to the correct clinical indication.

The appropriateness of prescribing donepezil, with no managed entry, was estimated from a published systematic review of the appropriateness of prescribing (5). This review summarized the main studies that explored this issue but did not present an overall published value for the prevalence of appropriate prescribing in England (18;33). These published data were used to approximate the level of appropriate prescribing without agreed managed entry policies. It was assumed that managed entry improves the appropriateness of prescribing.

Measuring Costs

Four components of resource use were costed. First, the resource use associated with the decision-making process of managed entry was identified. Resource use was identified from minutes of APC meetings, on-file letters of correspondence relating to the introduction of donepezil into practice at each Health Authority, and face-to-face interviews with each decision-maker involved with the managed entry of donepezil and named in the minutes of meetings. The time of each individual involved was costed using published national average pay scales. Travel costs were estimated from distance traveled multiplied by NHS public transport rate per mile (1;25). The costs of follow-up reviews and assessments of patients at clinics were not included in the model.

Second, the quantity and costs of donepezil prescribed were estimated from Prescribing Analysis and Cost (PACT) data and NHS Trust pharmacy department computer system data for the year 1997–98. PACT provides data on prescribing in general practice. It is collected centrally following the reimbursement of community pharmacists and dispensing doctors for dispensing NHS prescriptions. Third, the cost of formal health and social care for

Alzheimer's disease was estimated from published estimates (NHS Executive burdens of disease) for dementia (code ICD-9) (23). This was combined with published prevalence data to estimate the costs of mild to moderate Alzheimer's disease for the population profile for each Health Authority (9;14;20;28). Fourth, it was estimated that appropriate prescribing of donepezil would reduce the number of in patient beds required by patients with Alzheimer's disease (31).

All costs were standardized to a base year (1997) when donepezil was licensed for use in the United Kingdom. Costs, with the exception of those relating to the decision-making process, were quantified for 1 year of resource use and valued in British pounds (£). The model therefore included the prescribing costs associated with a maximum of 1-year's treatment with donepezil. The costs associated with the decision-making process were discounted (6% discount rate) if they exceeded 12 months.

Measuring Outcomes

The survey indicated that decision-makers monitored the use of donepezil with clinical measures used in trials to demonstrate safety and efficacy. These included the ADAS-Cog to test the severity of impairment in selective areas of cognition (29). It was intended to collect clinical effectiveness data from the hospital medical notes for all patients initiated on treatment in the study sites in 1997–98. However, these data were incomplete and of variable quality. Therefore, clinical effectiveness was estimated as an improvement of −2.61 (95% confidence interval: −3.45 to −1.79) points on the ADAS-Cog scale (measured on a 70-point scale), based on the results of a meta-analysis of three trials (2). This was converted to a percentage value ($2.61/70 \times 100$). For an average dose of 5 mg per person per day (based on the clinically recommended dose), the outcome was 3.7% (95% CI: 2.6% to 4.9%) improvement for the patient population, when donepezil was appropriately prescribed (i.e., in accordance with clinical indications or guidelines). If donepezil was prescribed inappropriately, or appropriately not prescribed, the outcome was assumed to be status quo with no change in the ADAS-Cog score. Side effects as a result of receiving donepezil were assumed to be negligible. If a patient population was not prescribed donepezil and this was inappropriate, disease progression was set equal to the expected annual decline in cognitive function (6–12 ADAS-Cog points per year) for a person with mild to moderate Alzheimer's disease (31).

The minimum decline of 6 ADAS-Cog points was used as a conservative estimate for the main analysis. This gave an incremental outcome measure for the cost-effectiveness analysis of unit per cognitive function gained (estimated as a 1% increase in ADA-Cog score). However, this measure does not give information about the likely benefit or value of differences in cognitive function. Two additional outcome measures were defined. These were the number of patients with a clinically important change in cognitive function and quality-adjusted life-years gained (QALYs). A change of 4 points (5.7%) in the ADAS-Cog was used to estimate the number of patients with a clinically important change in cognitive status with and without donepezil (32).

To value changes in health, published utility data for health states associated with Alzheimer's disease were combined with the endpoints of progression from mild to moderate levels of illness to estimate QALYs. The only available published utility values were estimated from 679 caregivers of patients with Alzheimer's disease, using the Health Utilities Index mark 2 (HUI2) and mark 3 (HUI3) (21;22). There is evidence to suggest that proxy valuations of utility are lower than patients' actual values (11;26), which means that the analysis will underestimate the value of improvements in patients health and overestimate the value of any decline in patient's health.

The HUI3 utility data were used for the main analysis. The impact of using utility scores generated from HUI2 rather than HUI3 was tested in the sensitivity analysis. If

Table 3. Baseline Values Assigned to the Probabilities

Probability	Baseline value		
	001	007	010
Managed entry effective	.46	.46	.46
Prescribed donepezil given managed entry effective	.02	.04	.06
Prescribed donepezil given managed entry not effective	.18	.18	.18
Prescribed donepezil, no managed entry	.18	.18	.18
Donepezil prescribed appropriately given managed entry effective	.69	.61	.68
Donepezil not prescribed appropriately given managed entry effective	.69	.61	.68
Donepezil prescribed appropriately given managed entry not effective	.34	.34	.34
Donepezil not prescribed appropriately given managed entry not effective	.34	.34	.34
Donepezil prescribed appropriately given no managed entry	.34	.34	.34
Donepezil not prescribed appropriately given no managed entry	.34	.34	.34

donepezil was prescribed, or not prescribed, appropriately, then the published utility score associated with mild Alzheimer's disease was used. This assumed that the appropriate use of donepezil delayed disease progression, and patients were maintained in their current state of mild disease.

If donepezil was prescribed, or not prescribed, inappropriately, then the utility score associated with moderate Alzheimer's disease was used. This assumes that patients deteriorate from mild to moderate disease as a result of inappropriate prescribing.

QALYs were estimated for two cases: a) if donepezil was prescribed, or not prescribed, appropriately, disease progression from mild to moderate illness would be delayed by 12 months; and b) disease progression would only be delayed by 6 months.

RESULTS

Probability, Cost, and Outcome Data

The probability values for each model are summarized in Table 3. The costs associated with the decision-making process for each Health Authority are summarized in Table 4. These costs were discounted at a rate of 6%. The impact of changing the discount rate to 3% and 5%, respectively, is shown. The choice of discount rate did not affect total costs.

The model assumed that 56% of patients with Alzheimer's disease would have mild or moderate disease (9). The number of expected patients with mild to moderate Alzheimer's disease was 1,447 in site 001, 1383 in site 007, and 2617 in site 010. There was insufficient data to estimate the distribution of patients over different stages of disease severity and costs per stage. An average cost of £1,929 was applied to the predicted number of patients to generate the cost for the population in each Health Authority. The average cost was based on the costs per year of managing a Health Authority population of patients with mild to moderate or severe Alzheimer's disease (9;14;20;23;28).

Table 4. Summary of Variable Costs Associated with the Decision-making Process of Managed Entry

Study site	Time cost	Travel cost	Total cost (undiscounted)	Total cost[a] (discounted)
001	£2,424	£27	£2,451	N/A
007	£2,719	£288	£3,007	N/A
010	£10,862	£1,113	£11,975	£11,944[b]

[a] Discount rate = 6%.
[b] Total cost at 3% discount rate = £11,970; total cost at 5% discount rate = £11,950.

Table 5. Utility Values and Estimated QALYs

Endpoint	Utility values		QALYs			
	HUI3 Mean (SD)	HUI2 Mean (SD)	HUI3 12 months	HUI3 6 months	HUI2 12 months	HUI2 6 months
Donepezil prescribed, or not prescribed, appropriately	0.39 (0.24)	0.69 (0.16)	0.39[a]	0.29[c]	0.69[a]	0.61[c]
Donepezil prescribed, or not prescribed, inappropriately	0.19 (0.20)	0.53 (0.17)	0.19[b]	0.19[d]	0.53[b]	0.53[d]

[a] Estimated as (utility value for mild Alzheimer's disease × 1).
[b] Estimated as (utility value for moderate Alzheimer's disease × 1).
[c] Estimated as (utility value for mild Alzheimer's disease × 0.5) + (utility value for moderate Alzheimer's disease × 0.5).
[d] Estimated as (utility value for moderate Alzheimer's disease × 1).

The total costs for donepezil prescriptions, in 1997/98, were: £8,309 for study site 001, £4,501 for study site 007, and £12,862 for study site 010. The cost savings associated with reducing inpatient stay by prescribing donepezil were estimated as £619,886 (study site 001), £592,469 (study site 007), and £1,500,236 (study site 010). This was based on the variable costs of an estimated decrease in inpatient stay of 6 months and annual in patient stay costs (23;31). Table 5 presents the utility values attached to the model endpoints.

Expected Costs and Outcomes

Overall, the process of managed entry of donepezil was associated with higher expected costs and higher expected outcome than no managed entry (Table 6). The 95% confidence intervals for the net expected costs and net expected outcomes are relatively narrow and do not cross zero. These would suggest that the differences between managed entry and no managed entry for donepezil are statistically significant. The incremental cost-effectiveness ratios for managed entry of donepezil indicate that, compared with no managed entry, there were substantial differences between the different models used in the three study sites. The expected cost per unit of cognitive function gained (estimated as a 1% increase in ADAS-Cog score) ranged from £18,000 in study site 001 to £28,000 in study site 010.

DISCUSSION

This study indicates that the process of managed entry was resource-intensive (hypothesis 1). The results also indicate that the time costs of the process vary between the three models evaluated. Comparison of the local and national rates of prescribing donepezil as well as the results of the national survey suggest that the process were effective in influencing prescribing practice (hypothesis 2). The available data suggest that managed entry was associated with appropriate prescribing in the study sites. However, there was limited data to estimate the probability of appropriate prescription or nonprescription of donepezil without managed entry. The lower rate of prescriptions for donepezil and the higher probability that it was prescribed appropriately suggest that managed entry reduced the costs of the drug (hypothesis 3). In addition, the analysis indicates that managed entry increased health gain associated with appropriate prescribing of donepezil (hypothesis 4). However, all the models of managed entry were associated with net expected costs, with an incremental cost effectiveness ratio of £18,000–£28,000 per unit of cognitive function gained compared with no managed entry.

Table 6. Expected Costs, Outcomes, and Incremental Cost-effectiveness Ratios Associated with the Decision-making Process of Managed Entry

	Health Authority		
	001	007	010
Baseline expected costs			
Managed entry[a]	£2,770,000	£2,645,000	£6,690,000
No managed entry[a]	£2,755,000	£2,632,000	£6,664,000
Net difference[a]	£15,000	£13,000	£25,000
Mean net expected cost (n)[b]	£14,927 (1,000)	£12,431 (1,100)	£25,282 (1,300)
95% confidence interval[b]	£14,365–£15,489	£11,901–£12,961	£23,980–£26,584
Baseline expected effectiveness			
Managed entry[a]	−3.57%	−3.83%	−3.51%
No managed entry[a]	−4.43%	−4.43%	−4.43%
Net difference[a]	0.86%	0.60%	0.92%
Mean net expected effectiveness (n)[b]	0.847% (700)	0.584% (1,000)	0.947% (900)
95% confidence interval[b]	0.816%–0.878%	0.557%–0.610%	0.917%–0.976%
Incremental cost effectiveness ratio [net expected costs/net expected effectiveness][a]	£18,000 per % change in ADAS-Cog	£22,000 per % change in ADAS-Cog	£28,000 per % change in ADAS-Cog
Baseline expected QALYs[c]			
Managed entry[a]	0.290 QALY	0.283 QALY	0.289 QALY
No managed entry[a]	0.258 QALY	0.258 QALY	0.258 QALY
Net difference[a]	0.032 QALY	0.025 QALY	0.031 QALY
Mean net expected outcome (n)[b]	0.03 QALY (1800)	0.03 QALY (3200)	0.03 QALY (1800)
95% confidence interval[b]	0.023–0.041 QALY	0.017–0.033 QALY	0.024–0.041 QALY
Incremental cost per QALY [net expected costs/net expected QALYs][c]	£470,000 per QALY	£520,000 per QALY	£8,070,000 per QALY
Sensitivity analysis			
Incremental cost-effectiveness ratio – assuming 5.7% change in ADAS-Cog is clinically significant	£140,000 per % change in ADAS-Cog	£170,000 per % change in ADAS-Cog	£230,000 per % change in ADAS-Cog
Incremental cost per QALY			
HUI3 scores & 6-month delay in disease progression	£940,000 per QALY	£1,090,000 per QALY	£15,700,000 per QALY
HUI2 scores & 12-month delay in disease progression	£580,000 per QALY	£6,50,000 per QALY	£10,000,000 per QALY
HUI2 scores & 6-month delay in disease progression	£1,150,000 per QALY	£1,300,000 per QALY	£19,300,000 per QALY

n = number of iterations.
[a] Calculated from the baseline decision analysis.
[b] Estimated from the probabilistic sensitivity analysis.
[c] Estimated using HUI3 scores, assuming that donepezil delays disease progression for 12 months.

Decision makers need to consider a number of factors when interpreting the incremental cost-effectiveness ratios of managed entry versus no managed entry. These include the local decision-making context and constraints, the range and relative value of process and patient outcomes, and uncertainty in the data used for this analysis. This model specifically evaluated the managed entry of donepezil using a decision analytic framework. A survey of decision makers identified donepezil as a drug targeted for managed entry. At the time of its

product launch, the data on clinical effectiveness were limited. Furthermore, donepezil was perceived to have a potentially large impact on the Health Authority's drug budget because of an anticipated high volume of use in the patient population. Donepezil is typical of drugs targeted for managed entry in that it had the potential to impact on the Health Authority drug budget. However, the results of this case study may not be directly generalizable to the introduction of other types of drug into practice. The model used in this paper could be made more generalizable to reflect the introduction of different types of drugs by changing the values assigned to the probability, cost, and outcome variables defined in the decision tree.

The results of this case study were specific to three Health Authorities in NorthWest England nonrandomly selected as study sites. The nonrandom choice of study sites potentially biased the evaluation, since the nature of the sites influenced the implementation and impact of managed entry and therefore the results of the study. The study sites differed in terms of the total annual expenditure for each study site and the number of primary healthcare providers. It is possible that the different effects found for managed entry are due in part to the characteristics of these three Health Authorities rather than the type of managed entry adopted. It is not possible, therefore, to generalize directly from the results of these three study sites to other Health Authorities, which have different characteristics.

Decision-making Context and Constraints

This model focused on the work of APC, but the framework for the model could be applied to decision-making bodies based in NHS Hospital or Primary Care Trusts. Each APC took a very different approach to the managed entry of donepezil with different decisions about the introduction and use of the drug in practice. This was despite all APCs having access to the same sources of evidence on clinical effectiveness. The three approaches to managed entry of donepezil differed in terms of the length and complexity of the decision-making process. The relative length of the selected approaches to managed entry was a feature of the ease with which decisions were made, approved by the chief executives, and implemented. Health Authority 001 reached a decision relatively quickly, which was ratified by the chief executive. However, Health Authority 010 took longer to reach a decision, mainly because they decided to establish a new memory clinic, which required extensive negotiations between different staff of the Health Authority and relevant NHS Trusts. Furthermore, the number of individuals involved in the decision-making process added with the complexity of reaching a decision. These differences in approach affected the relative expected costs and outcomes of managed entry compared with no managed entry. However, the analysis did not address the question of whether the process of managed entry used by Health Authorities 001 and 007 was feasible or cost-effective in Health Authority 010.

Value of Outcomes

The value of outcomes was primarily measured using clinical endpoints, the ADAS-Cog, because this was the outcome measure decision makers' chose to evaluate the effectiveness of donepezil. A change of four points (5.7%) has been reported to be a clinically significant improvement in an ADAS-Cog score. Using this measure, the incremental cost-effectiveness ratios were £140,000 per person with a clinically important change in ADAS-Cog for study site 001 and £230,000 for study site 010. These results indicate that managed entry was not cost-effective.

Additional analyses explored the potential impact of managed entry using QALYs as a measure of health benefit. This provided preliminary information on the possible value of the process and outcomes of managed entry to participants and patients, which are important aspects of the assessment of cost-effectiveness. The incremental cost per QALY ranged from

£470,000 per QALY to £19.3 million per QALY. This analysis also indicates that managed entry is unlikely to be value for money compared with other healthcare technologies.

However, the data available for this modeling study were uncertain. In particular, proxy valuations from the carers of patients were used, which could underestimate the impact of managed entry on the QALY measure and overestimate the incremental cost-effectiveness ratio. In addition, the analysis excluded other valued outcomes of donepezil (such as the utility to carers) and managed entry, such as the value of engaging a range of healthcare professionals in discussion about the use of new drugs. For example in this evaluation, pharmacists were the key individuals involved with the design and implementation of local drug policies. However, other healthcare professionals and Health Authority staff were involved from, for example, finance and contracting departments. Although each individual had a defined role in the decision-making process, it was considered necessary to take a team approach to develop each Health Authority's plan of action for introducing donepezil.

Data

This study aimed to record outcome data on the clinical effectiveness of donepezil. This was attempted, but the data were not readily accessible. Incorporating effectiveness rather than clinical efficacy data would have given some measure of the effect of noncompliance on the outcome of prescribing donepezil. Databases had been developed in two of the NHS Trusts for donepezil. Pre-assessment scores for donepezil were usually recorded, but follow-up scores were often not available. The quality of monitoring the use of donepezil was variable and not sufficient to calculate the effectiveness of the use of donepezil in practice for the three study sites.

There was a variety of published literature that addressed the difficult issue of the prevalence of appropriate prescribing in the United Kingdom (6). There were different perceptions on the definition and implementation of the concept of appropriateness with respect to prescribing. This study assumed a prevalence value of 34% using published data, which defined appropriateness in terms of clinical indication. Managed entry was assumed to affect the level of appropriate prescribing in this model. Decision makers based in the NHS should therefore be clear whether they believe their managed entry policy does improve the appropriateness of a drug's use in clinical practice before they relate the results of this study to their own practice.

Two estimates were included in the cost calculations, which valued the effectiveness of donepezil in reducing institutionalization care. There was uncertainty attached to these values. This study used the only published estimate on the effect of donepezil on institutionalization, which was not from an RCT of the drug. The actual effectiveness of donepezil in reducing institutionalization was not known. The sensitivity analysis indicated that the effectiveness of donepezil had to increase considerably before managed entry was successful in terms of minimizing costs. The analysis indicated that a drug has to be known to be effective in removing the need for other forms of care before it is worth managing its entry into practice, if the objective is to minimize healthcare costs.

The best available estimates of unit costs were used to quantify the financial impact of the process of managed entry. The cost of illness estimates in the managed entry model assumed a uniform cost distribution for managing mild, moderate, or severe Alzheimer's disease. Recent publications give treatment costs for patients with Alzheimer's disease of different degrees of severity and confirm that it is relatively more expensive to manage a patient more severely affected by the disease (16). Therefore, the figures used will not give an accurate picture for Health Authorities with a different distribution of mild, moderate, and severe disease in the population of people with Alzheimer's disease.

Local managed entry policies appeared to affect the use of donepezil. The estimated expected uptake of donepezil was higher than actual use, suggesting managed entry restricted the uptake of donepezil. Other factors, such as individual consultant or general practitioner prescribing behavior, may affect the uptake of donepezil into practice. In addition, the prevalence data on mild to moderate Alzheimer's disease, the population eligible for donepezil, were not of good quality. Furthermore, not all patients with mild to moderate Alzheimer's disease may be eligible for donepezil due to comorbidity with, for example, asthma or obstructive airways disease. The number of patients eligible for donepezil may therefore have been overestimated.

This is a preliminary study designed to identify the key pieces of information required to evaluate the value of managed entry. Further research is required to assess the empirical validity of this model as a tool for quantifying the economic impact of the managed entry of new drugs. However, the results of this study suggest that there are potentially quantifiable differences in the costs and outcomes associated with managed entry. Managed entry may be a worthwhile mechanism to introduce drugs into practice. However, poor accessibility and availability of data present serious obstacles for both researchers and policy makers. This economic evaluation used published effectiveness data that indicated managed entry could maximize health gain to a defined patient population. However, 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. Decision-makers therefore could not have known the effect of their decisions on the health of the local patient population. This modeling study did not assess the quality of the guidelines produced. A recent study indicated that clinical guidelines produced on donepezil did not fulfill the criteria for high-quality evidence-based guidelines (13).

POLICY IMPLICATIONS

The National Institute of Clinical Excellence may be helpful in providing good quality, timely information to assist the production of evidence-based guidelines. However, this study has highlighted an important practical implication. To improve managed entry and associated production of clinical guidelines, decision-makers must establish systems to monitor the impact of their drug policies. The current system of recording patients' diagnosis and clinical management on paper records separate from non–patient-linked prescribing data does not facilitate monitoring of drug policies. Electronic medical records and electronic prescribing may help to monitor the rate and appropriateness of medicine use. These benefits of moving from paper to electronic records will only be realized if accurate clinical diagnosis is recorded and linked to the route, dose, and quantity of prescribed medication.

REFERENCES

1. Automobile Association. *A to B*. London: Automobile Association; April 1999.
2. Birks JS, Melzer D. Donepezil for mild to moderate Alzheimer's disease. *The Cochrane Library.* 1999;issue 1;1-14.
3. Briggs A, Sculpher M. Sensitivity analysis in economic evaluation: A review of published studies. *Health Econ.* 1995;4:355-371.
4. Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: The role of sensitivity analysis. *Health Econ.* 1994;3:95-104.
5. Buetow SA, Sibbald BS, Cantrill JA, Halliwell S. Prevalence of potentially inappropriate long term prescribing in general practice in the United Kingdom, 1980–95: Systematic literature review. *BMJ.* 1996;313:1371-1374.
6. Buetow SA, Sibbald B, Cantrill JA, Halliwell S. Appropriateness in health care: Application to prescribing. *Soc Sci Med.* 1997;45:261-271.

7. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation: A practical approach. *Med Decis Making*. 1985;5:157-177.
8. Dyer O. Multiple sclerosis drug prompts rationing fears. *BMJ*. 1995;311:969.
9. Ely M, Melzer D, Brayne C, et al. *The cognitively frail elderly: Estimating population characteristics and needs of people with cognitive disability, including dementia*. Report to the NHS Executive Mental Health Research & Development Programme. 1995.
10. Fitzpatrick RW. Is there a place for Drug and Therapeutics Committees in the new NHS? *Environ Health Perspect*. 1997;3:143-147.
11. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-effectiveness in health and medicine*. New York: Oxford University Press, 1996.
12. Guyatt GH, Cook DJ, Sackett DL, Eckman M, Pauker S. Grades of recommendation for antithrombotic agents. *Chest*. 1998;114 (suppl):441s-444s.
13. Harvey RJ. A review and commentary on a sample of 15 UK guidelines for the drug treatment of Alzheimer's disease. *International Journal of Geriatric Psychiatry*. 1999;14(4):249-256.
14. Hofman A, Rocca WA, Brayne C, et al. The prevalence of dementia in Europe: A collaborative study of 1980–1990 findings. *Int J Epidemiol*. 1991;20:736-748.
15. *International medical statistics*. Pinner: International Medical Statistics; August 1998.
16. Kavanagh S, Knapp M. Cognitive disability and direct care costs for elderly people. *Br J Psychiatry*. 1999;174;539-546.
17. Kelly C, Harvey R, Cayton H. Drug treatments for Alzheimer's disease. *BMJ*. 1997; 314:693-694.
18. Kurji KH, Haines AP. Detection and management of hypertension in general practices in North West London. *BMJ*. 1984;288:903-906.
19. Leach R, Leach S. Drug and therapeutics committees in the United Kingdom in 1992. *Pharmaceutical Journal*. 1994;253:61-63.
20. Melzer D, Hopkins S, Pencheon D, Brayne C, Willimas R. Dementia. In Stevens A, Raftery J, eds. *Health care needs assessment*. Vol 1. Oxford: Radcliffe Medical Press; 1994:chapter 16.
21. Neumann PJ, Hermann RC, Kuntz KM, et al. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. *Neurology*. 1999;52:1138-1145.
22. Neumann PJ, Sanberg EA, Araki SS, et al. A comparison of HUI2 and HUI3 utility scores in Alzheimer's disease. *Med Decis Making*. 2000;20:413-422.
23. NHS Executive. *Burdens of disease*. Leeds: NHS E;1991.
24. NHS Executive. *Purchasing and prescribing*. Leeds: NHS E; 1994. EL(94)72.
25. NHS Executive North West. *Travel expenses*. Leeds: NHS E; 1998.
26. Novella JL, Jochum C, Jolly D, et al. Agreement between patients' and proxies' reports of quality of life in Alzheimer's disease. *Qual Life Res*. 2001;10:443-452.
27. Payne K. *The economic impact of decision-making in relation to the introduction of drugs into practice*. Manchester: University of Manchester; 2000.
28. *Population estimates unit*. London: Office of National Statistics;1998.
29. Rosen WG, Mohs RC, Davies KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141:1356-1364.
30. Rous E, Coppel A, Haworth J, Noyce S. A purchaser experience of managing New expensive drugs: Interferon beta. *BMJ*. 1996;313:1195-1196.
31. Stein K. *Donepezil in the treatment of mild to moderate senile dementia of the Alzheimer type*. Report to the Development and Evaluation Committee. 1997;69:1-35.
32. Stein K. *Rivastigmine in the treatment of senile dementia of the Alzheimer type*. Report to the Development and Evaluation Committee. 1998;89:1-37.
33. Stern D. Management of hypertension in twelve Oxfordshire general practices. *J R Coll Gen Pract*. 1986;36:549-551.
34. Wakeman A, Leach R. Joint prescribing committees: Characteristics, progress and effectiveness. *Health Trends*. 1997;29:52-54.