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What Price Depression?
The Cost of Depression and the Cost-Effectiveness of Pharmacological Treatment

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The purpose of this study was twofold: to measure the overall direct costs of depression for 1990 in the UK, and to develop a model to illustrate issues in the evaluation of the relative cost-effectiveness of the pharmacological treatment of depression. We compared a tricyclic antidepressant, imipramine, with paroxetine, a newer antidepressant. For assessing the cost of illness, we used a top-down approach. We calculated direct but not indirect costs. Cost-effectiveness was evaluated by developing a simulation model based on the theory of clinical decision analysis to compare the costs and outcome of each treatment. From this we estimated the expected cost per patient and the cost per successfully treated patient. The total cost to the nation of depressive illness was estimated to be £222 million. The expected costs per patient were found to be similar for paroxetine and imipramine (£430 v. £424). The costs per successfully treated patient were found to be lower for paroxetine (£824) than for imipramine (£1024). The results were stable when a sensitivity analysis was applied to the variables employed in the model. The most sensitive variable was the cost of treatment failure. Our model thus reveals that medication that appears expensive in terms of cost per day may not be so when patient compliance and the total costs of treatment are taken into account.

Over the course of a year, some 100 million people worldwide develop episodes of clinical depression (Sartorius, 1975). There are those who argue that the prevalence is increasing (Schwab *et al*, 1979; Klerman, 1988), particularly as certain high-risk subgroups are becoming more predominant in the general population (Kramer *et al*, 1987). The social impact of depressive illness includes both the disability induced (Paykel *et al*, 1978; Weissman *et al*, 1978; Hurry *et al*, 1987), and the burden imposed on relatives (Fadden *et al*, 1987*a*,*b*). Although the social impact has been well documented, the same cannot be said of the overall economic cost to society, or of the socio-economic consequences of treating depression with pharmacological agents.

In the present cost-conscious health care environment, it is not surprising that formulary committees, physicians, pharmacists and health care providers – and indeed the general public – are now interested in the cost-effectiveness of new and apparently expensive treatments. However, opportunities to undertake this form of evaluation are limited, for three reasons. First, cost-effectiveness is a novel criterion in therapy and, for most new drugs, no specific evaluation of cost-effectiveness has been carried out because the clinical work was planned many years before the need for this type of data became clear. Second, cost-effectiveness relates to the efficient use of the drug in normal practice; when a drug is first launched, no such data are available. Third, the data needed for economic evaluations are scarce in the health care system; there is no systematic collection of data on costs of treatment for individuals or groups of patients with a defined diagnosis.

We have attempted to study the economic aspects of depressive illness in two complementary ways: by estimating the overall economic cost of depression for 1990 in the UK, and by developing a model that permits the calculation of the cost-effectiveness of treatment with different pharmacological agents. The first exercise gives an indication of the economic significance of the obligation to treat depression, and thus provides the context for the evaluation of cost-effectiveness.

Rationale and method

Cost of depression in the UK

Definitions and sources of data

For the purposes of this study, we chose to define depression as in codes 296 and 311 of the *International Classification of Disease* (ICD-9) (World Health Organization, 1978). The ICD-9 also contains the category 300.4, 'neurotic depression', but the UK Department of Health does not provide separate figures for this category, which is included under 'neuroses'. This inevitably means that our calculations are underestimates.

Incidence data and estimates of costs were obtained from the Department of Health, the Office for Population

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Censuses and Surveys (London), and the British Medical Association (London), using published and unpublished data. Cost data within the National Health Service (NHS), before hospitals became self-governing trusts, are largely notional, but represent a best estimate of the actual costs involved.

Method of costing

In order to estimate the economic burden of depression in the United Kingdom, we have used the cost-of-illness method, based on the human capital theory (Hodgson & Meiners, 1982). It is well established and straightforward, but three methodological issues have to be considered: (a) whether to base the study on the prevalence or the incidence of the disease; (b) whether to analyse the data using a top-down or bottom-up approach; and (c) whether to include indirect costs in the calculation.

Prevalence and incidence. It is crucial to decide between approaches based on prevalence and on incidence. The cost of illness in relation to the *prevalence* of the disease takes account of all cases existing during a given year, and all resources used for prevention, treatment and rehabilitation, or lost as a result of morbidity and mortality within that year. Loss of production due to disability and death occurring during the year is measured as the present value of all future production.

By contrast, cost of illness based on *incidence* looks at those cases of the disease developing for the first time in a given year. Future costs and loss of production are calculated in terms of present values.

Cost of illness based on incidence has the advantage of highlighting the consequences of changing the occurrence of the disease, and is best applied to an investigation of preventive treatment, where the benefits can be measured as the number of cases avoided. Cost of illness based on prevalence has the advantage of relating to measures of total annual health care expenditure, and this is particularly relevant for a recurrent disease like depression, where treatment is needed for long periods. This consideration led us to select the prevalence approach.

Top-down v. bottom-up methods. The '*top-down*' approach to calculating cost of illness partitions the total national cost of illness between different diseases: for example, the total number of hospital admissions or bed-days is classified according to the frequency of the different diagnoses. The '*bottom-up*' approach usually starts from a defined sub-population with the chosen disorder and registers all costs of illness related to it; the costs for the subpopulation are then extrapolated to give an estimate for a total population.

There are advantages and disadvantages to both methods. The method we chose, the top-down approach, requires good data on the use of health care resources, and, if indirect costs are included, on illness-related absenteeism and disability in relation to the specific diagnostic group. Its disadvantages are that it relates directly to the total health care costs of the disease without extrapolation, and avoids the risk of double counting. However, the method may be inaccurate when diagnoses are under-reported or mis-reported, as is the case with depression.

The bottom-up method concentrates on the selection of a group of patients who can be thoroughly investigated; this involves a greater risk of double counting, and the added disadvantage of having to define a representative population before results can be extrapolated.

Direct and indirect costs. A further methodological issue concerns direct and indirect costs. *Direct costs* are the costs of detection, treatment, prevention, rehabilitation and long-term care arising from depression. In theory, all relevant health care and non-health care costs are included, but in practice there is a limit to what can be identified and measured. Most studies concentrate on the costs of hospitalisation, out-patient care and drugs. It is important to decide whether specific therapeutic or diagnostic interventions, such as treatment with electroconvulsive therapy, should be costed as a part of overall hospital care. Similarly, hospital treatment given to out-patients can be included either as hospital care or as out-patient care; we have chosen to include such interventions in the cost of out-patient care. Estimates of drug costs were derived from prescription cost analysis data supplied by the Department of Health (Prescription Pricing Authority, 1988). All drugs prescribed for depression (ICD-9 codes 296 and 311) were included in the calculation. Direct costs should be included regardless of whether the patient, the government or some other institution is paying.

Indirect costs arise from the loss of production of the patients due to short-term illness, permanent disability and premature death. A further element is the loss of production of family members taking care of the patient. There are several problems connected with the measurement of these costs. Most concern the relationship between the salaries used to calculate loss of production and the actual value of lost production. A further difficulty in estimation is that morbidity and mortality related to suicide are not included under ICD-9 codes 296 and 311, but under codes 800–999 (injury and poisoning).

Although the estimation of indirect costs is problematic, they are important and are almost certainly higher than direct costs. The lack of reliable data for calculating indirect costs led us to focus our analysis on the direct cost of depression. We recognise, however, that the inclusion of indirect costs would be likely to multiply the advantage shown by more effective treatments.

Cost-effectiveness of pharmacological treatment

Method of costing

The establishment of cost-effectiveness requires a comparison, either between treatment and no treatment, or between different types of treatment. In this study, we have compared two generations of antidepressant treatment, represented by imipramine, a tricyclic antidepressant, and by paroxetine, one of a new class of serotonin re-uptake inhibitors. Tricyclics are cheap and effective when used at full therapeutic doses, but have troublesome side-effects. New generation antidepressants are also effective, but comparatively expensive. One of their main advantages is relative freedom from side-effects. Although this is not at

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first apparent, side-effects have an important bearing on cost-effectiveness.

There are three possible strategies for generating information about the costs and benefits of antidepressive treatment. The first is an economic evaluation linked to a comparative clinical trial. This option was not open to us since a prospective clinical trial would take at least two years to report. Moreover, clinical trials do not accurately reflect routine clinical practice. A second strategy would be to observe the respective treatments in clinical practice. This was not feasible either as it depends on the availability of marketed drugs. There are very strong arguments for implementing both these strategies in the future to increase the sophistication of cost-effectiveness calculations. However, as an interim approach, we chose to develop a third strategy, a simulation model based on the theory of clinical decision analysis (Weinstein & Fineberg, 1980). This method has four steps: identify and define the decision problem; describe the structure of the decision problem over time; identify the information needed; and choose a course of action. Models like this have been used by others to study the cost-effectiveness of antidepressants (Hatziandreu *et al*, 1992).

A decision tree (Fig. 1) was constructed to represent the logical and temporal sequencing of the clinical problem, and so provide a model of clinical practice. We assumed that the physician's aim is that his/her treatment would achieve a successful outcome, and this enabled us to estimate the expected cost for each treatment strategy and the cost per successfully treated patient (a measure of cost-effectiveness). If the first choice of treatment is successful, the costs incurred include the cost of the course of treatment – in this case using paroxetine or imipramine – and the cost of the general practitioner's visits. We allowed for the possibility that successfully treated patients may relapse, and we counted patients who responded to a second course of the drug as successfully treated. We further assumed that a switch of drug (from imipramine to paroxetine and vice versa) took place if the original treatment choice was not successful; thus, all treatment failures incurred a cost of one course of imipramine and one course of paroxetine. The model represents different pathways leading to the final outcome, the pathways being determined by what happens to individual patients at each nodal point. Each pathway will be followed by a given proportion of patients in treatment.

The model used data from different sources, in particular the results from phase III clinical trials, and was assumed

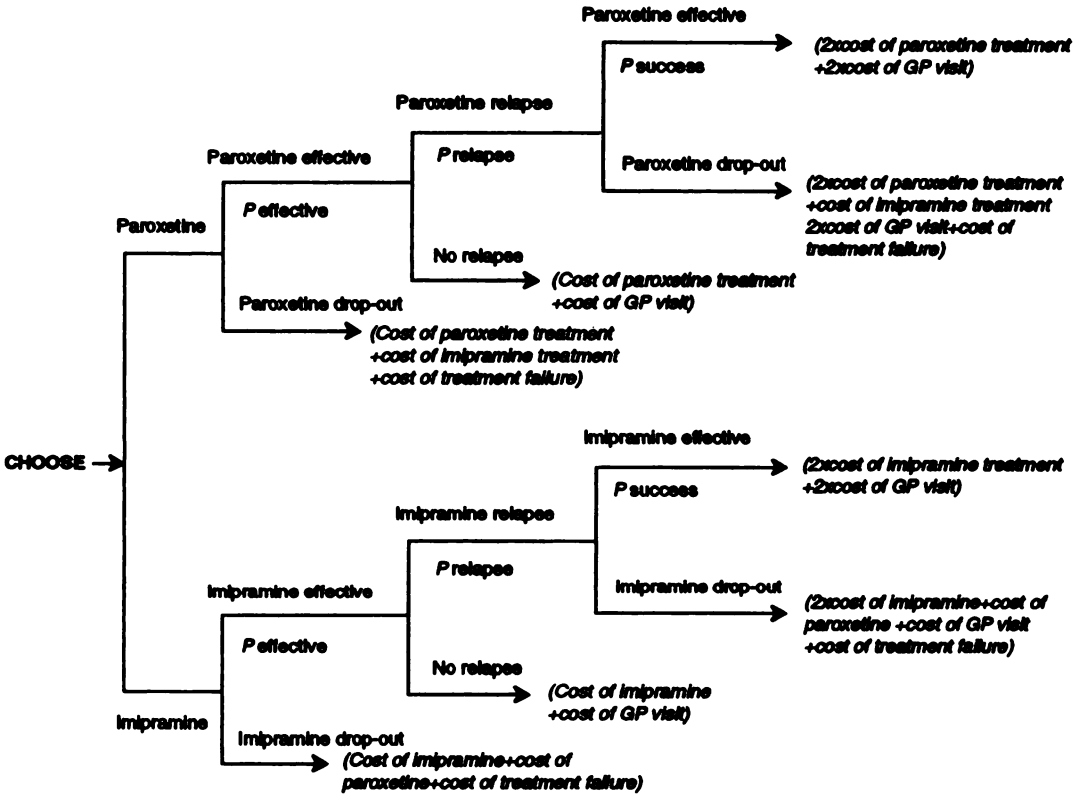


Fig. 1 Model simulating clinical practice over 12 months. From Jönsson & Bebbington (1993), reprinted by permission of John Wiley & Sons Ltd, ©1993.

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Table 1
Overview of reasons for drop-out from intention-to-treat sample (reproduced with permission from Dunbar *et al*, 1991)

Reasons for drop-out	Paroxetine ($n=240$) No. (%)	Placebo ($n=240$) No. (%)	Imipramine ($n=237$) No. (%)
Lack of efficacy	25 (10)[1]	79 (33)	17 (7)[3]
Adverse events	55 (23)[1,2]	21 (9)	85 (36)[3]
Other	22 (9)	28 (12)	25 (11)

1. Fisher's exact test, paroxetine-placebo difference, $P \geqslant 0.001$.
2. Fisher's exact test, paroxetine-imipramine difference, $P \geqslant 0.001$.
3. Fisher's exact test, imipramine-placebo difference, $P \geqslant 0.001$.

to cover a period of 12 months. One important factor is the difference in the drop-out rate between patients on paroxetine and on imipramine. We assumed a drop-out rate of 54% for imipramine and 42% for paroxetine (Table 1), based on a pooled analysis of six randomised, double-blind, placebo-controlled studies carried out in the USA involving 726 patients treated for a period of 6 weeks, one of the largest studies conducted with paroxetine to date (Dunbar *et al*, 1991). These data were considered to be more extensive, and thus probably more reliable, than other available sources; it was shown that significantly more imipramine-treated patients than paroxetine-treated patients dropped out as a result of side-effects.

The pooled analysis showed no difference in anti-depressant effect between paroxetine and imipramine in patients who were compliant. For the sake of simplicity, therefore, we did not include failure to respond to treatment

Table 2
Results from the questionnaire sent to the panel of experts

Variable	Values used in model	Range of results given by panel
1. Average length of a primary course: weeks	12	8-12
2. No. of GP visits	6	5-6
3. Probability of relapse: %	25	20-30
4. Patients successfully treated by further course: %	60	40-80
5. Drop-outs successfully treated: %	60	50-60
6. Drop-outs becoming in-patients: %	5	5-6
7. Average length of stay of in-patient drop-outs: days	14	14-21
8. Patients attempting suicide: %	-[1]	1-4
9. Drop-outs - no. of visits to GP	10	6-12
10. Drop-outs attending at out-patients: %	5	5-6
11. Drop-outs receiving psychotherapy: %	4	2-4
12. No. of psychotherapy sessions	6	5-6
13. Drop-outs receiving ECT: %	1	-[2]
14. No. of sessions of ECT	6	-[2]

1. Not included in model.
2. All panel members in agreement.

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in the model. Our expression for the effectiveness of treatment was thus simplified to one based purely on compliance, being calculated as $(1-d)$, where d is the drop-out rate (see Table 4). In other words, we assumed that if patients did not drop out due to side-effects or lack of effect, their treatment was successful. This over-simplification carries the assumption that pharmacological failure affects both groups equally (Dunbar *et al*, 1991). The patients were assumed to receive the drugs for 12 weeks.

To bridge the inevitable gaps in the information required by the model, data about patient management and treatment patterns were estimated by a panel of experts (Table 2). A questionnaire was sent to eight clinicians (consultant psychiatrists or general practitioners who specialised in psychiatry) selected for their known expertise in the management of depressed patients. Five of the panel then met to review the results of the questionnaire, clarify the questions and answers, and produce a final report. The members of the panel thus had the opportunity to compare their answers and discuss similarities and differences. However, there was no obligation to achieve consensus, and members of the panel gave their own answers.

The results of the panel were corroborated in discussions with six psychiatrists, six hospital pharmacists and three groups of eight general practitioners; interestingly, none expressed doubts about the panel results.

We calculated the expected cost per patient for paroxetine and for imipramine by multiplying the costs for each potential outcome in the model by the probability of the outcome occurring. The probabilities included the drop-out rates for the two drugs, the relapse rate, and the probability of successful treatment following relapse. The expected cost for each treatment alternative can be interpreted as the average or typical cost, given no knowledge of which path the patient will take in the tree (Fig. 1). The expected cost was thus dependent on both the probability of, and the cost associated with, the different pathways in the model.

Costs for suicide attempts were not included because of the low incidence (1-2%) and the small overall contribution to direct cost. Daily treatment costs were taken as £0.20 for imipramine and £1.13 for paroxetine (this had been reduced by 18% at the time of going to press). The cost of treating depression in general practice was based on a 15-minute consultation, since it was assumed that this illness would consume more time than an average consultation with a general practitioner (7½ minutes). The cost of home visits was not included in the model.

To simplify the presentation of data in the model, the results of the expert panel (Table 2) are combined with the unit cost data (from Jönsson & Bebbington, 1993) to give the costs associated with treatment failure (Table 3). For example, the panel estimated that only 5% of treatment failures would end up in hospital, and they were likely to stay there for around 14 days (that is, less than the median for all psychiatric diagnoses). The hospitalisation costs associated with treatment would thus be 5% of 14, multiplied by the price per hospital day. Despite its infrequency, hospitalisation therefore made an appreciable contribution to overall costs. However, visits to general practitioners and out-patient psychiatric clinics accounted for most of the cost of

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Table 3
Calculation of the cost of a treatment failure

Item of cost	Calculation	Total (£)
GP visit	10 visits @ £20	200.00
Out-patient visit	5 visits @ £36	180.00
Hospitalisation	0.05 × 14 × £132	92.40
Psychotherapy sessions	0.04 × 6 × £50	12.00
Electroconvulsive shock treatment	0.01 × 6 × £60	3.60
Total		488.00

treatment failure. Psychotherapy and electroconvulsive therapy costs were trivial, due to the very small probabilities associated with these outcomes.

We also calculated the *marginal cost-effectiveness* for paroxetine and conducted a sensitivity analysis of variations in effectiveness of the two drugs (Jönsson & Bebbington, 1993). Marginal cost-effectiveness provides an estimate of the price to be paid for the additional effectiveness of the more effective treatment. It is thus the most relevant measure for decisions about resource allocation. So, if the cost to the health care system of one more successfully treated patient is, say, £200, are we actually prepared to pay this price?

Marginal cost-effectiveness can be understood by a motoring analogy. If a motorist has the option of buying a 100 mph car for £10 000 or a 120 mph car for £14 000, the cost per mph of the first car is £100, while that of the second car is £116.70. The cost per *additional* mph is, however, £200. This is the equivalent of marginal cost-effectiveness, and allows the motorist to decide if this is a reasonable price to pay for additional speed. As the price of the second car is brought down, additional speed costs less and so the marginal cost-effectiveness diminishes. Indeed, if the faster car only costs £9 999, it offers higher speeds at less cost. Translating this back into the language of our study, this is equivalent to the point at which a drug comes to offer better treatment at lower cost. The drug is then said to *dominate*.

The values we have chosen for the calculations in our model are in some cases merely best guesses. Clearly, our conclusions lose force if small changes in these values make considerable differences to the results. On the other hand, it is possible that the overall results are robust in the face of quite large differences in individual values. The sensitivity analyses allow us to see how closely our conclusions are dependent on the chosen values.

Results

Cost of depression

The direct costs of depression in the UK at 1990 prices was estimated to be £222 million. This was derived from the unit costs and total number of events in 1990 (Jönsson & Bebbington, 1993), together with a total drugs bill of £41 722 200 (Prescription Pricing Authority, Department of Health, 1988).

Estimates have been extrapolated to the country as a whole by assuming that the uptake of different services is geographically uniform and constant over time. The calculation of hospital costs was based on the assumption that the needs of psychiatric patients for care, investigation and treatment were uniform. However, needs are likely to vary according to diagnosis in an unknown manner, so that the average cost per day may be an under- or overestimate of the real costs consumed by patients with depressive illness.

Cost of pharmacological treatment

Expected costs per patient

The model showed that the expected costs of treatment per patient irrespective of outcome were similar for the two drugs, namely, £430 for paroxetine and £424 for imipramine. Given that paroxetine costs five or six times as much as imipramine, this is a very small difference, and can be attributed to the greater tolerability and resulting effectiveness of paroxetine.

Comparative cost-effectiveness

The cost per successfully treated patient per year under the model was used as the measure of cost-effectiveness. The average cost per successfully treated patient was actually lower for paroxetine (£824) than for imipramine (£1024) (Table 4), implying that paroxetine was more cost-effective than the older, less well tolerated treatment.

This result was very stable. In the sensitivity analysis we found that when the end-of-range values were substituted in place of the mean values, the overall cost per treatment changed very little (Jönsson & Bebbington, 1993). We had some difficulty in obtaining values for the cost of a day in hospital for depressed patients. The figure we initially used in the model is the average cost for all bed-days in the National Health Service (NHS). Twenty years ago the cost of a bed-day within the psychiatric services was much less than the cost of a general medical bed. However, the vast majority of acutely ill psychiatric patients are now accommodated in district general hospitals (DGH), and such beds may be as expensive as general medical beds in the same hospitals. Moreover, because the number of beds in large mental hospitals has declined, the persistence of fixed costs means that the cost of a bed-day in such hospitals has increased. Because of the uncertainty over this issue, we obtained costings from nine hospitals chosen to represent the range of costs likely to be met, from acute admission wards in an older psychiatric hospital, through DGH psychiatric wards, to beds in teaching hospitals. The range of costings was surprising, from £91 to £300 per night (as might be expected, two of the three highest values were contributed by teaching hospitals); the median value was £117. These costs included bed, board and basic care, but not medical or drug costs. We conducted a sensitivity analysis specifically in relation to bed costs per day. If we reduced the cost of one day's stay in hospital from £132 to £91, it made very little difference to the cost per treated patient: this became £407 for imipramine and £416 for

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Table 4
Cost-effectiveness in relation to the relative effectiveness of paroxetine

Efficacy ($1-d$)	Expected cost per patient: £		Cost per successfully treated patient: £		Marginal cost effectiveness: £
	Imipramine	Paroxetine	Imipramine	Paroxetine	
0.50	424	453	1024	1008	823
0.52		448		956	440
0.54	↓	442	↓	909	249
0.56		436		865	134
0.58		430		824	58
0.60		42 4		785	3
0.62		412		750	Dominate[1]

1. Dominate = the point at which one treatment (paroxetine) offers better effectiveness at lower cost.

paroxetine. At a hospital bed cost of only £50 per day, the cost per treated patient was £390 for imipramine and £403 for paroxetine, while the cost per successfully treated patient was £953 for imipramine and £772 for paroxetine. Even at zero cost for bed-days, the model still predicts a lower cost per successfully treated patient for paroxetine.

The most sensitive variable analysed was the cost of treatment failure; using the highest value (£700), paroxetine had a lower expected cost per patient (£531 v. £548). However, using the lower value (£300), the expected cost per patient was only 10% lower for imipramine (£314 v. £340).

The results are, however, considerably more sensitive to the relative effectiveness of the drugs. Table 4 shows how average and marginal cost-effectiveness change when the effectiveness of paroxetine is altered and that of imipramine is kept constant. The effectiveness obtained in the multi-centre clinical trial of paroxetine reported by Dunbar *et al* (1991) is such that the drug is close to giving better results at lower cost, as can be seen from the values for marginal cost-effectiveness.

Discussion

The establishment of criteria for effectiveness and safety has significantly increased the quality of therapy. With the introduction of newer and better tolerated (more effective), but also more expensive, drugs comes an obligation to document their potential economic impact.

Cost-of-illness methodology gives a way of evaluating the cost of new treatment. Such studies can show which illnesses consume most resources and, consequently, the potential for reducing costs with more effective treatments. This approach has been used, for example, to evaluate the introduction of cimetidine into the treatment of ulcer disease (Jönsson, 1983; Jönsson & Carlsson, 1991).

There have been three major criticisms of cost-of-illness studies: that they do not address a specific question about value for money; that they lack justification in terms of a generally accepted or clearly defined theory of social welfare; and that they ignore changes in the quality of life. This has led some authors to conclude that such studies are useless to policy makers, since they measure the 'benefits of the unattainable' (in the sense that it is impossible to eliminate all the costs of a disease), or are misleading because they show a bias in favour of the working population and the rich (Shiell *et al*, 1987).

We think, however, that the cost-of-illness approach can be effectively defended with the argument that some information is better than none (Hodgson, 1989). All economic evaluations are aimed at *assisting* decision-making: they do not actually prescribe the decision to be made. It is, therefore, important to know the costs related to a specific disease like depression and the potential savings from new developments in treatment, even if it is impossible to measure their impact accurately before they are introduced.

In evaluating the cost-effectiveness of treatment directly, the outcome measures chosen will determine what type of evaluation can be undertaken (see Drummond *et al*, 1982). We chose a short-term model, in which the aim was to arrive at a successful outcome of treatment, and thus to estimate the cost per successfully treated patient. In longer-term models, the prevention of relapse or suicide can be used as the outcome measure, permitting the cost per life-year gained to be calculated (e.g. Hatziandreu *et al*, 1992). It is then appropriate to take quality of life into account (Mehrez & Gafni, 1989); however, this method is also more demanding since it requires long-term follow-up data. In future, it should be possible to set up cost-effectiveness evaluations as part of clinical trials, and collect relevant economic data simultaneously; indeed, one such study is currently under way (Lönnqvist *et al*, 1992).

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In our present study, depression was defined as categories 296 and 311 of ICD–9, which clearly underestimates the actual burden of depressive illness. If category 300.4 (neurotic depression) were included, the number of admissions would increase by approximately 25% (Bebbington, 1987), and the discrepancy would be even greater for out-patient and general practice attendances.

There is clear evidence that much depression goes unrecognised (e.g. Freeling *et al*, 1985; Hurry *et al*, 1987; Bridges & Goldberg, 1988). This is likely to increase the indirect costs of depressive illness. It probably also has an effect in increasing the direct costs, as depression is likely to consume treatment resources even if physicians fail to make the correct diagnosis. However, it is very hard to put a figure on this.

Calculations of the cost of depression give relevant information about the economic aspects of the disease. We were not happy about the UK data for calculating indirect costs, and we thus decided to limit our estimates to direct costs. The total direct cost of depression for the UK in 1990 was just over £200 million. About 50% of the cost was related to hospitalisations and about 25% to drugs. Our value is likely to underestimate all but the drug costs, although it is unlikely to be less than half the actual figure.

Four other publications furnish estimates of the direct costs of treating depression, two from the US and two from the UK (Stoudemire *et al*, 1986; Rice, 1992; West, 1992; Kind & Sorensen, 1993).

Stoudemire and his colleagues (1986) made a systematic attempt to estimate the cost of depression to the US economy at 1980 prices. They arrived at a value of $2.1 billion per year for direct costs, but in comparing these figures with their UK counterparts one must take into account the fivefold population difference, the difference in *per capita* GNP and the fact that the US spends twice the proportion of GNP on health care that the UK does.

West (1992) obtained a value for direct costs in Britain of £333.3 million. His method for calculating this was considerably less detailed than the one we employed, although his results are reasonably commensurate with ours.

A still higher value – £417 million – was obtained by Kind & Sorensen (1993). This did include costs of social services as well as of direct health care, but the former only accounted for £40 million. The major discrepancies between their figures and ours lie in their considerably higher estimates for hospital admission (£165 million) and general practice attendance (£126 million).

Finally, Rice (1992) has reported another estimation of costs from the US at 1985 prices. She came up with the very high figure of $12.17 billion for direct costs alone. Even applying our rule of thumb of dividing by 10 to compare with UK figures, this remains by far the highest value for direct costs.

Three of the studies also made an attempt to calculate a value for indirect costs (Stoudemire *et al*, 1985; Rice, 1992; Kind & Sorensen, 1992). The first and last of these agree that indirect costs are likely to be perhaps seven times as much as direct costs. Thus, Stoudemire *et al* (1986) made separate evaluations of levels of morbidity and mortality, years of productive activity lost, and years of life lost. On the basis of their estimates, those authors obtained values of $10 billion per year in total morbidity costs due to lost productivity, and $4.2 billion as the total cost of increased mortality. Even these figures were thought by the authors to be 'lower-bound' estimates.

Rice (1992) reports rather different results. While her estimate for direct costs is very high, her figure for indirect costs is disproportionately low, so that they contribute only 42% to the overall cost of $20.8 billion (1985 prices). She also calculated that affective disorders were responsible for 21% of the total cost of mental illness in the UK in 1990.

The low value for the indirect costs of depressive illness in this report is clearly related to the method used to derive them. Rice applied multiple regression analysis to the ECA programme data (Robins & Regier, 1991). However, morbidity due to affective illness in the ECA survey was greater in higher-outcome groups, with the consequence that loss of earnings was compensated for in the analysis by the higher income of those suffering the disorder. This seriously vitiates the credibility of the values obtained.

The only British attempt to assess indirect costs is that of Kind & Sorensen (1992), using methods similar to Stoudemire *et al* and obtaining similar results. Their estimate of indirect costs at £2973 million was 7.1 times as great as their estimate of direct costs (above).

These calculations can only be very approximate: nevertheless, the striking similarity of the ratio of indirect to direct costs as obtained by Stoudemire *et al* (1986) and by Kind & Sorensen (1992) – about 7:1 in each case – does support the idea that the former greatly exceed the latter. As indirect costs multiply overall costs, so they increase the significance of studies of cost-effectiveness.

From our cost-effectiveness analysis of anti-depressant treatment, we estimate the expected cost per treated patient, for a 12-month period, to be £420–430. If we assume that about 1% of the UK population require treatment for depression each

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year – that is, about 0.5 million patients – this would give a direct annual cost for depression of £210–215 million, an estimate strikingly close to the value we obtained from our top-down cost-of-illness calculation. In fact, the annual treated prevalence is likely to be closer to 2%, emphasising that our figures represent a minimum estimate of the cost of depression.

Although paroxetine costs five or six times as much per day as imipramine, the efficacy and improved tolerability of paroxetine appear to compensate for this. We based our calculations on the large study by Dunbar *et al* (1991), who showed that more patients treated with imipramine than with paroxetine dropped out due to side-effects and, furthermore, that the difference in the percentage of adverse events occurring in each group mostly favoured paroxetine.

Song and his colleagues (1993) have recently published a meta-analysis comparing tricyclic and related drugs with selective serotonin re-uptake inhibitors (SSRI) including paroxetine. Drop-out rates were used as a measure of tolerability. The analysis used pooled data from a heterogeneous group of patients who took part in 63 randomised controlled trials utilising different protocols. Paroxetine was compared with amitriptyline in six of these studies, with imipramine in three, with clomipramine in two, and with doxepin and mianserin in one each. The overall comparison with imipramine gave a drop-out rate of 39.5% for paroxetine and 47.4% for imipramine, a difference of 8%. However, the comparison between paroxetine and any non-SSRI gave drop-out rates that were much more similar: 30.8% for paroxetine and 31.8% for the other compounds.

There are, of course, considerable difficulties in using a meta-analysis of this type to estimate the size of effects, as there are quite clearly wide differences in the definitions employed (demonstrated in the striking variability of drop-out rates between studies) and in the attention given to drop-out rates by Song *et al*, whose main focus was on efficacy. Our decision to use the results from Dunbar *et al* (1991) was made on the basis that they performed their analysis on an intention-to-treat basis on a large data set obtained from pooling results from six centres using an identical protocol.

The difference between paroxetine and imipramine in expected cost per patient treated was negligible. The cost per *successfully* treated patient (those who did not drop out) was actually lower for paroxetine than for imipramine (£824 v. £1024). In these terms, paroxetine thus appears more cost-effective than imipramine. The results were sensitive to the relative effectiveness of paroxetine, but even if the drop-out rate for paroxetine were as high as 50%, it would still have a lower cost per successfully treated patient.

Our results were generated within a simulation model, combining data from clinical studies with panel-based opinions about patient management and unit-cost data from the NHS. The model is not intended as a particularly accurate description of the way depressed patients are treated in the UK today; indeed a one-to-one mapping – that is, modelling all the potential pathways to treatment outcome in the real world – would be immeasurably complicated. Our model does, however, contain sufficient information to illuminate important issues in comparative cost-effectiveness. It emphasises that compliance is a crucial element in the cost-effectiveness of treatment, and that expensive preparations may not make for expensive treatments if patients are more willing to stick to them. This gives the treating physicians an economic defence for drugs they choose to prescribe from humane motives.

Despite the strong assumptions on which it is based, the values generated by our model may in practice be reasonably realistic: our estimated cost of treatment failure can be compared with the estimate by McCombs *et al* (1990) of about $1000, which was based on data from the California Medicaid programme, 1983–88.

Our model serves as a first attempt at cost-effectiveness analysis in the field of antidepressant treatment. It certainly emphasises the crucial need for better insights. These will only be obtained from fully empirical studies. Ideally, such studies should include documentation about direct and indirect costs, together with patien s' functioning and quality of life. They should also cover a relevant time period (possibly more than one year), and the full range of pharmacological and non-pharmacological alternatives. It is clear from our findings that drop-out rates are a crucial element of treatment costs and that, in future studies of efficacy, much more attention must be given to the operational definition of treatment failure. Only through systematic studies of this type can we acquire the information for a rational choice of treatment based on the cost-effectiveness of competing treatments.

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