

Cost-Effectiveness of SSRIs: A European Perspective

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Abstract

Background: Evaluating treatments for depression is of great importance given that estimates of lifetime prevalence range up to 20 per cent. The class of antidepressants known as Selective Serotonin Reuptake Inhibitors (SSRIs) has been a major innovation in this area, but has also raised questions about their cost-effectiveness as a first-line treatment, due to their high price compared to other drugs.

Aims of Study: The study aimed to contribute to this debate, from within the context of European health care systems. These systems share a common set of pressures to contain costs, many of which, in Europe, are funded from public finances, unlike the US system, with its greater private sector involvement.

Methods: A range of published papers were reviewed. They all covered the general area of costs and SSRIs and were evaluated in a European context.

Results: Some studies have considered the possible use of SSRIs purely as a matter of accounting costs. Not surprisingly, they have argued against switching, on the grounds of high acquisition costs. However, studies based alongside clinical trials have incorporated efficacy into the analysis. They have produced cost-effectiveness or cost utility based arguments in favour of the SSRIs or other innovative, high-price antidepressants.

Another approach has used retrospective analysis of real patients' experience of treatment. This has shown that, if the full costs of treatment are considered, there is an argument for switching from Tricyclic Antidepressants (TCAs) to first-line use of SSRIs.

Most economic evaluations have used decision analysis techniques and thus are subject to all the qualifications that apply to such modelling exercises. With only one exception, all the studies in this category were in favour of switching to newer antidepressants. While efficacy was generally accepted as roughly equal, the newer products were seen as less toxic and better tolerated. The consequence was savings in health care costs that outweighed the increase in drug acquisition costs.

Discussion: The economic evaluation papers in this review have almost all challenged the view that health care providers should regard SSRIs as 'too expensive' for widespread use. Instead, if one integrates clinical outcomes with a full range of health care costs the high-price products may be more cost-effective. Certainly that is the message from this review, although the observations must be qualified, as most of the studies considered were UK based.

Conclusions: In all health care systems there are now incentives to control costs, which may act as a disincentive to the use of SSRIs, but if those responsible for drug budgets also have financial responsibilities outside the drug budget they will also have an

incentive to control those areas. In this case, there is a body of evidence to suggest they would gain by switching to SSRIs.

Implications for Health Care Provision and Use: Decisions on favoured classes of antidepressant for first-line treatment should not be made purely on the basis of drug costs. The implications for all aspects of health spending should be included in the deliberations.

Implications for Health Policy Formulation: The impact of spending across all budgets should be considered when drawing up policy on the use of new health care technologies, such as the SSRIs.

Implications for Further Research: Most studies in this area have used modelling techniques, which are subject to a number of limitations. They have also used results taken from the artificial environment of clinical trials. Future research should aim to generate economic evaluations based on effectiveness amongst real patients in clinical practice. © 1998 John Wiley & Sons, Ltd.

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Introduction

The debate on the cost-effectiveness of SSRIs is taking place within a general consensus on the wide prevalence of clinically significant depression. It is a chronic disease and a recent review pointed out that most patients who recover from depression will go on to experience a recurrence¹ while lifetime prevalence has been estimated at a range of figures varying from 6 per cent² up to figures over 20 per cent.

Recognition of the scale of the problem has coincided with an expansion in the range of pharmaceutical treatments available, of which SSRIs constitute only one part. Acquisition prices of these antidepressants vary considerably: in a recent UK price guide, a daily dose varied from about £12 per week for the most expensive new product, down to approximately 10p for the cheapest generic TCA³ with similar variations in many other European countries. However, there are many other costs associated with treating depression, such as psychiatrist interventions, outpatient clinic attendance and hospital admissions.

In calculating the full costs of treating depression, the generally acknowledged keys are the tolerability of treatments and patient compliance.⁴ This raises an important question: whether there are significant differences between SSRIs and other categories of antidepressant, such as the TCAs. One recent review⁵ emphasized that there were perceived differences in the incidence and severity of side-effects. Despite higher acquisition costs for the new drugs, they

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could be cost-effective if the inclusion of non-medication direct costs reduced the comparative total burden on healthcare providers or on society. That is, if changes in non-medication costs compensate for any increases in acquisition costs. The authors, working from a US perspective, found that only one clinical trial⁶ had set out to tackle the economic question, with all other evaluations being retrospective or modelling exercises.

It is regrettable that currently there is little research on cost-effectiveness in this area, especially given the interest shown by public authorities such as the UK Department of Health (DoH)⁷ and the US Public Health Service.⁸ As yet European authorities have not gone as far as health services in Canada or Australia in demanding evaluations, but existing recommendations have given strong incentives for such work. For example in France, pricing negotiations, at the licensing stage, may include consideration of an economic evaluation, and the UK DoH guidelines have attempted to create standards for comparisons and institute some common principles.

There are many issues to be resolved before such common principles can be agreed on⁹ and several areas and categories of decision where evaluation can be used. These differ in several respects, one important division being between those targeted at demand-side decisions i.e. the actions of those generating demand for drugs, such as doctors, pharmacists and patients, and those aimed at supply-side factors, influencing the behaviour of those who are marketing products.

- (i) *Treatment guidelines, issued by public authorities or the medical profession, on preferred options in particular disease areas.* Their use depends critically on evaluations being accepted by clinicians.
- (ii) *Decision making in healthcare organizations.* In this instance, the use made of evaluations will depend on the economic incentives affecting the organization. There are few healthcare organizations in Europe with economic imperatives as sharply defined as those of US Health Maintenance Organisations (HMOs), but incentives do apply nonetheless.
- (iii) *Approval decisions.* SSRIs have been introduced quite recently and have gone through European licensing regimens based only on clinical principles. For a variety of reasons, it is perhaps advisable that such decisions remain beyond the scope of economic evaluations.
- (iv) *Reimbursement decisions.* It is more realistic to use pharmacoeconomics data to make decisions on whether new products should be reimbursed from public finances. This is explicit in the Australian system and perhaps signalled for the future in the NHS Limited List of products that will not be reimbursed. Such decisions may vary between different illness groups.
- (v) *Pricing decisions.* The level at which drugs may be priced or reimbursed may also be determined by

evaluation, used to establish a point where marginal social benefit is equal to marginal social cost.

Some economic principles are already being incorporated in the practice advice being given to health care providers. One recent UK review¹⁰ set out quite explicitly to answer questions regarding cost-effectiveness of SSRIs, as distinct from the questions on efficacy and drop-out that were tackled by prior meta-analyses.^{4,11} The authors dismissed all available cost-effectiveness studies as flawed and imperfect and concentrated on yet another systematic review of available published clinical evidence. As they identified no significant clinical differences, they argued that use of SSRIs would generate substantial increases in health care costs.

Most tellingly, they related SSRIs to the NHS budget for new treatments and innovations. In 1994 it stood at £187 million, while an estimate of the additional prescribing costs of switching from TCAs to SSRIs¹² was £162 million. Hence, Hotopf *et al.*¹⁰ concluded that switching to SSRIs as first-line antidepressants would absorb 87 per cent of this budget and was therefore not necessarily good value for money.

The European Perspective

Within Europe there are wide variations in methods of health care finance and pharmaceutical pricing and reimbursement systems. While there may be no unifying philosophical principle in European health care systems, there has been a common imperative since the late 1980s: a process of reform motivated by a need to control costs. In all countries public authorities have attempted to control pharmaceutical prices, as part of this drive to control overall health care expenditure.¹³ This led one set of commentators to observe that 'Europe offers a diverse laboratory of experiences for examining the potential impact of health policies on the pharmaceutical industry'.¹⁴ This is the context for assessing the current set of evaluations of SSRIs and related products and their role in influencing both demand-side and supply-side factors.

Economic Evaluations

A wide range of papers report economic evaluations from a European perspective, although most of those reviewed in this paper offer a UK perspective. There have already been some reviews of the pharmacoeconomic literature on the case for SSRIs,^{1,5,15} tending to adopt a clinical perspective in their critiques. One key question they ask is whether recent, innovative drugs should be routinely used in the treatment of depression and, if so, whether they should be first-line treatments.

Evaluations Alongside Clinical Trials

The 'gold standard' for clinical evaluation has long been the randomized clinical trial. This has led to pressure for economic parameters to be included in trials, facilitating

Table 1. Clinical trial based studies

Authors	Antidepressants evaluated	Period of analysis	Economic evaluation method	Prescribing recommendation
Bisserbe <i>et al.</i>	sertraline fluoxetine	6 months	cost analysis	sertraline > fluoxetine
Sintonen <i>et al.</i>	fluoxetine moclobemide	6 weeks	CEA CUA	moclobemide > fluoxetine

economic evaluation alongside the clinical evaluation, but some questions have been asked about the issues surrounding this move (see, for example, Gray *et al.*¹⁶). Particular problems have arisen with the question of statistical power and the differing numbers of patients required to show statistically significant differences: cost differences require far larger numbers to achieve the same power as clinical differences, as there tend to be more outliers and wider variations within groups. Nonetheless, some studies have been produced that have directly evaluated clinical trials. Two recent examples from a European context are shown in **Table 1**. Their results are summarized in **Table 2**.

Bisserbe *et al.*¹⁷ based their study in France and started from the assumption that SSRIs can provide cost savings compared to TCAs, as a consequence of better tolerability. Hence, they moved on to compare two SSRIs, sertraline and fluoxetine. At the final visit, 231 patients were still eligible for assessment (116 sertraline and 115 fluoxetine). Clinically, there were no differences between the two groups after a six-month double-blind randomized controlled trial (RCT). There were also no statistically significant differences in baseline clinical or demographic characteristics. However, data were also collected on resource usage and direct and indirect costs: in these areas there were differences. The indirect costs were not clearly defined, but appear to refer to production losses associated with time lost to depressive illness. Direct costs were calculated on two bases:

(i) 'societal costs', defined as full prices charged;

(ii) 'insurance costs', defined as the sum actually reimbursed.

The division between these two approaches is necessary because in the French system patients must pay for costs of care and then reclaim money from the social insurance system, which will reimburse a fixed proportion of the full price, which may well be less than 100 per cent. Hence cost-effectiveness may vary depending on which perspective is adopted, society or the insurance system, even though the focus remains on direct costs in both cases.

The fluoxetine group showed higher health care resource usage, mainly due to more frequent consultations with physicians, and greater absences from work. Consequently, in both direct and indirect costs, the sertraline group incurred lower costs than fluoxetine patients. This study restricted itself to comparing mean costs. No power calculations or confidence intervals were provided for the costs, nor were they combined with the outcome data to provide cost-effectiveness data. Consequently the analysis leaves unanswered some critical questions concerning the cost implications of switching between use of the two drugs evaluated. It also does not explore potential variations in effectiveness between the societal perspective on costs and a view focused only on costs to be reimbursed by insurance: obviously, if the numerator in ratio calculations is varied, then the final answer will change. In fact, the whole definition of societal costs appears uncertain in this evaluation: in most places the societal cost is defined as the full price charged in the

Table 2. Bisserbe/Sintonen summary of results

Bisserbe <i>et al.</i>	Mean costs over 6 months	Cost savings: sertraline vs fluoxetine
sickness insurance	3079	288
total social costs (all costs in 1993 French francs)	8241	926
Sintonen <i>et al.</i>	Cost utility over 6 weeks	
	fluoxetine	sertraline
cost per patient having better quality of life at 6 weeks than at baseline	27.5	16.9
cost per average time weighted quality of life gain (one extra day at full quality of life) (all costs at 1000 Finnish marks, 1991)	32.1	15.5

private medical system. This may not necessarily be equal to the full social opportunity cost of a particular service.

Sintonen *et al.*¹⁸ take a very different approach in their evaluation. The study uses data collected alongside a six-week double-blind RCT comparing fluoxetine and moclobemide, a reversible inhibitor of monoamine oxidase-A (RIMA). After randomization, the study allocated 108 patients to the fluoxetine group and 102 to the moclobemide group. The end conclusion is that significance is found only in the indirect costs, basically informal care costs and production losses. When utility measures were included, quality of life based analysis was used to argue that prescribing should switch to the moclobemide regime. However, given the short period of clinical analysis there must be some question over whether to act on the recommendations of this study. This question is particularly applicable to the indirect costs within the economic study: six weeks is unlikely to be long enough for lasting effects on informal care and productivity to be observed. There were also a number of other issues with the clinical trial, such as the absence of a placebo group and the lack of detail on what actual doses patients were receiving, but, for prescribers, the main question concerns the absence of long-term evidence on moclobemide, the innovative comparator product. Patients are unlikely to be treated for six weeks only, hence more long-term data may be required before making decisions. This applies strongly to the quality of life data, as this concept only exists over time, so a short period makes it particularly difficult to be confident of estimates and extrapolations.

Retrospective Evaluations

In response to the lack of availability of clinical trials and also to questions of efficacy and effectiveness,¹⁹ retrospective studies have been produced using naturalistic data, but where do all the data come from for this type of analysis? One frequently used source is publicly available databases, such as MEDIPLUS in the UK or HMO computer archives in the USA. Alternatively, researchers may use retrospective collection of data from clinicians regarding their treatments and patient outcomes. This approach was used in a recent study by Forder *et al.*,²⁰ where patients receiving sertraline were identified from a previous open study of treatment in general practice²¹ and then matched against an equal number of TCA patients from the same practices.

Treatment with any TCA was acceptable, although most patients were treated with dothiepin (110), amitriptyline (43) or lofepramine (19). It was noticeable that of the three TCAs featured in some recent US studies^{22–24} only amitriptyline figured significantly in the UK. Only three patients received nortriptyline and no patients received desipramine.

Resource usage details were obtained by a postal survey of the participating GPs, who extracted information from their patients. The sertraline patients always showed lower mean costs, although none of the differences were statistically significant when *t*-tests were employed. More noticeable differences emerged when treatment outcomes, as assessed by the GPs, were introduced for cost-effectiveness comparisons

(Table 3). Measured against patients who were very much improved, or at least somewhat improved (based on a variant of the CGI), the same pattern emerged, with TCA patients recording much lower medication costs, with these outweighed by other areas of spending to show sertraline as the more cost-effective option.

At this level, evaluation of treatments for depression is producing fairly crude outputs from what was actually quite a rich data set. The authors developed their evaluation to perform multivariate analysis. They established a number of socio-demographic and treatment related items that were significant, but make the observation that 'There is no mechanistic way of selecting the "best" cost equation'. The interesting use that Forder *et al.* made of their model was to standardize for patient characteristic effect (generated by the sample) from the treatment effect (generated by use of either sertraline or TCAs). They re-estimated costs assuming that patient characteristics for each group remained unchanged, while their treatments were switched. The resulting predicted costs are shown in Table 4.

The patient characteristic effect accounted for only £1–£5 of the difference, while the treatment effect accounted for £112–£117. This line of analysis is important as it demonstrates the importance of treatment (sertraline or TCA) in accounting for costs rather than biases in the samples used. These effects do not translate into large differences in mean costs for the two treatment options, but they do support and emphasize the validity of the differences observed in cost-effectiveness. Measured by costs per successfully treated patient there was a large difference, and one which would justify switching from TCA use to SSRI use.

Decision Analysis Models

In the short term decision makers are faced with pressure to choose between available interventions before the results from prospective studies are available. Under these circumstances economic evaluation can use modelling techniques to assess the impact of treatment efficacies and resource usage on both costs and outcomes. Decision analysis is advocated in the Department of Health guidelines⁷ as a means for clarifying the process of care. This technique breaks 'complex problems down into manageable component parts and analyses those parts in detail' (Thornton *et al.*,²⁵ p. 1099; see also Stewart²⁶). A decision tree is a flow diagram representing the effects of decisions in terms of the probabilities of consequent events. Decisions and events are displayed in the order of occurrence. Where events are subject to chance a range of probability values can be employed to predict the likely impact of decisions on future events. The use of such techniques has been reviewed in other areas (see e.g. Glick *et al.*²⁷) but not yet in psychiatry. There are some criticisms of its use however, despite the problems that have already been mentioned concerning evaluations alongside clinical trials.¹⁶ In one recent critique, Sheldon²⁸ makes the point that most health research 'involves the use of some sort of modelling in order to abstract quantitative or qualitative information', thus even a double-

Table 3. Forder *et al.* Cost-effectiveness: costs per successfully treated patient (1993/94 prices, £)

Definition of cost	Patients very much improved			Patients at least somewhat improved		
	Sertraline (excluding drop-outs)	Sertraline (intention to treat)	TCA	Sertraline (excluding drop-outs)	Sertraline (intention to treat)	TCA
	Total cost (including informal care)	20 960	24 286	34 419	8581	9273
Total cost (excluding informal care)	20 259	23 493	32 760	8879	8970	10 682
Health and social care services plus medication cost	1 478	1 882	2 490	626	719	812
Medication cost	558	634	176	236	242	57

Table 4. Forder *et al.*, standardized (costs are £)

Treatment type	Sample		
	Sertraline	TCA	Significance of difference ^a
Sertraline	$C_{S.S} = 7724$	$C_{T.S} = 7725$	NS
TCA	$C_{S.T} = 7836$	$C_{T.T} = 7841$	NS
Significance of difference ^a	0.026	0.032	

^at-tests were employed.

blind RCT could be characterized as a model. This type of study makes a number of assumptions about patient selection and treatments offered, restricting both groups to a closely structured set, analysed and tested against a clearly defined set of hypotheses. Thus the use of decision analysis models is subject to a number of methodological issues.

A number of models of SSRI use are summarized in **Table 5**. They are all based in the UK, except for Le Pen *et al.*²⁹ (France) and Nuijten *et al.*³⁰ (Germany).

Jonsson and Bebbington³¹

This was the earliest in the series of studies above and evaluates the direct costs of using paroxetine or imipramine in the UK, from the perspective of the health care provider, the NHS. Clinical efficacy data were derived from selected RCTs and resource usage from a Delphi panel. A straightforward decision tree calculated direct health care costs over a one-year period, at 1990 prices. The expected costs, that is the mean cost per patient (on an intent-to-treat basis) were £430 for paroxetine and £424 for imipramine. Given the great difference in acquisition costs, this was an insignificant difference and was attributed to the greater tolerability of the SSRI, leading to greater effectiveness. The authors developed their analysis to offer cost-effectiveness comparisons on the basis of cost per successfully treated patient. The base case results here showed paroxetine at £824 having a clear advantage over imipramine at £1024, hence the recommendation was to switch prescribing from TCA use to SSRIs.

Their analysis has subsequently been criticized, for example on the grounds that clinical data were derived from selected RCTs, rather than the more objective process of systematic review.¹⁰ Particular attention⁵ has been drawn to the study

used to provide success rates:³² it shows results substantially more favourable to the SSRIs than earlier meta-analysis.

Hatziandreu *et al.*³³

This study took a rather more complex analytic. A Markov model (see Sonnenberg and Beck³⁴) was constructed to compare sertraline against dothiepin. Unlike Jonsson and Bebbington, the target patient group for this study were precisely specified (35-year-old women, history of depression etc). The model was then used to evaluate expected costs for the remaining lifetime of a cohort of these patients, making the step forward of comparing the standard episodic approach against the maintenance treatment that was perceived to be possible using SSRIs. An additional enhancement was to evaluate quality of life over the whole lifetime of the cohort. Years of life expectancy were converted to QALYs using utility weightings for health states associated with depression and treatment with antidepressants. The utility weightings were assigned by a panel of clinicians. The assumptions on the incidence and severity of side-effects led to the SSRI being measured as far better on a cost-utility basis and in fact sertraline was demonstrated to be better than many other health care interventions on a cost per QALY gained basis. Base case results showed an expectancy of 14.94 QALYs for sertraline patients against only 14.13 for dothiepin patients. At 1991 UK prices the lifetime costs were £3407 for sertraline and £1648 for dothiepin. The stress was placed on the incremental cost per QALY gained: this was £2172. At this level, the switch to sertraline use compared very favourably with other entries in a QALY league table.

However, there were limitations to this study. Relatively little long-term prospective data were available on mainte-

Table 5. Decision analysis studies

Authors	SSRI(s) evaluated	TCA(s) evaluated	Period of analysis	Economic evaluation method	Modelling technique	Efficacy data source	Sensitivity analysis	Switch TCA/SSRI?
Jonsson and Bebbington ³¹	paroxetine	imipramine	one year	CMA CEA cost of illness	decision tree	pooled results of clinical trials Delphi Panel	efficacies	yes
Hatzidreou <i>et al.</i> ³³	sertraline	dothiepin	lifetime (from age 35)	CUA	Markov chain	Delphi Panel	efficacies of utility values of health states resource costs discount rates compliance	yes
Stewart ³⁵	sertraline paroxetine	imipramine amitriptyline	one year	CMA CEA	decision tree	clinical trials meta-analyses	efficacies	no
Le Pen <i>et al.</i> ²⁹	fluoxetine	TCA (composite score)	eight weeks therapy one year health service savings	CMA CEA	decision tree	meta-analyses	social valuation of life-year resource costs efficacies probability of suicide attempt	yes
Kind and Sorensen ³⁸	all SSRIs (composite scores)	—	one year	CMA CEA	decision tree	pooled results of clinical trials	compliance rates efficacies	—
Montgomery <i>et al.</i> ³⁹		imipramine (also nefazodone)	six to eight weeks treatment one year follow up costs	CMA CEA	decision tree	results of double-blind RCT	costs of treatment failure relapse/effectiveness rates	switch TCA/ nefazodone
Nuijten <i>et al.</i> ³⁰	citalopram	doxepin trimipramine amitriptyline (composite score)	one year	CEA	Markov process	clinical trials meta-analyses	response rate relapse rate	yes

nance treatment of depression, which has been argued to add considerably to the model's inherent uncertainty.¹⁵ Furthermore, the utility weightings, which are so important when calculating QALYs, were evaluated by clinicians rather than patients, raising the possibility of some bias being present.

Stewart³⁵

..This study used the principles underlying the work of Jonsson and Bebbington,³¹ but expanded the decision tree to cover a more complex process. Instead of just one example of TCA or SSRI this model allowed for switching between use of two examples of each category. The analysis remained focused on the direct costs of health care only, but dissented from the other studies shown in the box, as the author concluded that there was no clear economic evidence for switching from TCAs to the first-line use of SSRIs. The base case figures for expected costs were actually very similar to those in the Jonsson–Bebbington evaluation. This time, expected costs were shown as

amitriptyline	£350.79
imipramine	£352.38
paroxetine	£386.31
sertraline	£401.36

As in the earlier study, all costs were very close and the order changed after calculation of costs per success:

amitriptyline	£539.00
imipramine	£491.25
paroxetine	£547.65
sertraline	£581.46

The results showed a cost advantage for remaining with TCAs, but the relative position was very close, certainly far closer than a comparison based on acquisition costs. This model has since been criticized for its interpretation of data from some of the source clinical trials,¹⁵ for using relatively low costs for treatment failures and, as in the work of Jonsson and Bebbington, assuming equal costs for delivery of treatment.⁵

Le Pen *et al.*²⁹

This study was based in France and took a very different approach from the three referenced above. Clinical data were sourced from a meta-analysis, comparing fluoxetine and a composite measure of tricyclics in common use in France. The authors constructed an 'event' tree, based on eight weeks of treatment. Their assumption that eight weeks was sufficient time to show significant improvement on the HAM-D scale is open to question. It is certainly a very short period from which to extrapolate long-term benefits. Differential rates of drop-out and other clinical events were used to construct a cost–benefit argument. Their conclusions acknowledge that switching from TCAs to SSRIs would involve a higher set of costs for French health care providers. The key to the decision is the level of valuation placed on a human life. Their model provides a threshold figure for this: if society's valuation is higher then the switch can be justified. Depending on the type of depression this threshold

varies from FF8600 (US \$1600) up to FF23 800 (US \$4500) at 1992 prices. Compared to other health care interventions these are relatively low costs per year of life saved, leading the authors to conclude that fluoxetine is a cost-effective intervention. However there are some reservations about the way they used suicide rates. Additionally, the period of treatment contributing to the marginal costs was only eight weeks, when most opinion now favours longer periods.^{36,37}

Kind and Sorensen³⁸

This evaluation also modelled the indirect costs and benefits of using SSRIs. It evaluated prophylactic care over a period of one year, comparing a composite set of SSRIs against an alternative strategy of watchful waiting. Prophylaxis resulted in higher direct health care costs and also a higher number of symptom free days, posing a question of whether the higher costs should be paid to achieve a higher level of health status. The authors leave this as an open question for society to answer. Their estimates of the one-year costs for a symptom-free patient, assuming a composite package of SSRIs, were between £389 and £474, lower figures than those produced by Jonsson and Bebbington³¹ or by Stewart.³⁵ The model evaluated symptom-free days as a key variable and thus facilitated calculation of indirect costs, measured by days of lost productivity. Their central estimate, for 1000 treated patients, was of annual benefits of £390 000. This underlies their suggestion that society should devote more expenditure to treatment of depression.

Montgomery *et al.*³⁹

In this study, the authors returned to the more straightforward decision analysis used by Jonsson and Bebbington.³¹ They took the model structure and treatment patterns used by that study and updated the resource costs, but more importantly substituted nefazodone (an SNRI) for paroxetine. This demonstrated the ease with which models can be manipulated to give revised analyses for different treatments. In this case there was also a change, in that actual data from a follow-up study were used to provide relapse figures for the one-year period of analysis. The consequence of this was that figures for efficacy and relapse were much improved on those used in the original study of Jonsson and Bebbington³¹ and so cost-effectiveness was much better, particularly for nefazodone.

There must be some question though as to the comparability of the data used, given the very large variations in relapse rates. The data used by Montgomery *et al.* provided very high efficacy rates and low relapse rates. Consequently, expected costs were £218 for nefazodone and £254 for imipramine, while the figures for successfully treated patients were £242 and £323 respectively. These figures are very much lower than those obtained for SSRIs or TCAs, in the studies reviewed earlier. As stated, they are lower because of the stronger assumptions of treatment efficacies. It is therefore difficult to use these figures for comparison against other studies, although the internal conclusion, that nefazodone is more cost-effective than imipramine, does appear to be robust.

Nuijten *et al.*³⁰

This paper once again evaluated a comparison of long-term maintenance treatment with an SSRI (citalopram) versus episodic use of a TCA. As with the study of Hatziandreu *et al.*³³ the outcomes were modelled using a Markov process, but this study was located in Germany and the time period was only one year. Clinical data were derived by a review of available published trials. Citalopram use resulted in an increase in mean time without depression and a consequent fall in direct medical costs, despite the higher acquisition costs of citalopram. Indirect costs were also estimated, as workdays lost, showing a further benefit associated with citalopram. The end conclusion was that the SSRI 'dominates' the TCAs, in that it provides better effectiveness at lower cost.

The results, expressed in 1993 DM, showed citalopram as the preferred outcome both in direct costs (DM3764 against DM4577 for TCAs) and indirect costs (DM4221 against DM7371 for TCAs). This derived from the estimated greater effectiveness of citalopram, measured as 8.2 months without depression against only 7.6 months for standard therapy. The perceived problems with this model focus on the use of data from short-term clinical trials as a basis for extrapolation to long-term treatment.

Discussion and Conclusions

The concluding question is, what is the European, or UK, perspective on SSRIs and other antidepressants? Regardless of geographical location, there are shared concerns with outcomes, clinical effectiveness and costs imposed on whoever pays for healthcare. These exist in all systems, irrespective of the details of provision or funding, and all European states make efforts, in different ways, to reduce prices. As pointed out earlier, throughout Europe, the period since the mid- to late 1980s has been characterized by continued efforts to control rising health care expenditures.

Into this context, SSRIs enter as yet another new, higher-price pharmaceutical innovation. In some analyses^{10,12} the higher price was used to make gloomy predictions about the potentially devastating impact that use of SSRIs would have on healthcare budgets. However, the studies reviewed in this paper have, in most cases, challenged these viewpoints and have argued that prescribers should switch away from older antidepressants. Despite the contrary arguments of some reviews and meta-analyses^{4,11} the studies have all argued that the new antidepressants show better results in terms of tolerability, side-effects or drop-outs. This applies to the literature based models (see Table 4) and also to the two evaluations of clinical trials.^{18,19} Perhaps more interestingly, this was also the conclusion of the paper by Forder *et al.*,²⁰ which was a retrospective study of patients in naturalistic settings. It was thus most appropriate as a guide for clinicians working with the substantial body of persons living in the community and requiring treatment for depression.

Forder *et al.* demonstrated the hypothesis on which the clinical trials and models were based: that improved outcomes

for patients would result in reduced resource usage, thus compensating purchasers for some or all of the expense of switching to use of SSRIs. From a societal perspective, there may be a potential economic benefit. However, whether this benefit can be realized and can act as an incentive for health care providers is a further question.

A key point is whether funders of drug budgets have incentives linked to other areas of spending, the areas where potential gains from SSRIs use will be realized. Some changes in financing systems may have weakened these links. In the UK, moves to GP fundholding have created incentives to reduce prescribing expenditure within each practice every year. However, gains from use of SSRIs, if they do accrue, will be outside that budget. Additionally, as shown by Hatziandreu *et al.*,³³ they may accrue over a long period, outside the time horizon of a prescribing budget or the planning horizon of a clinician.

In general, the opinion of published economic evaluations comes down in favour of SSRIs and other innovative antidepressants. However, there are problems in accepting this as an argument for clinicians across Europe to switch their prescribing patterns. Most of the studies use modelling techniques, as an area in which the underlying principles have been criticized.²⁸ Further research in the area should combine the best elements of evaluations alongside clinical trials and the principles applied retrospectively by Forder *et al.*²⁰ What is needed are evaluations in which clinical outcomes reflect effectiveness in naturalistic settings, rather than the model-driven efficacy of RCTs. As has been demonstrated,⁴⁰ the treatment received in clinical practice is often very different from that received in clinical trials, and, to optimize the benefits of economic analysis, the resource usage patterns should be those of real patients, not just participants in clinical trials or the ideal types produced by Delphi panels.

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References

1. Guze BH. Selective serotonin reuptake inhibitors: assessment for formulary inclusion. *PharmacoEconomics*, 1996; **9**: 430–442.
2. Reiger DA, Boyd JH, Burke JD *et al.* One month prevalence of mental disorders in the United States. *Arch. Gen. Psychiatry*, 1988; **16**: 977–986.
3. *Monthly Index of Medical Specialities*. September, London: Haymarket, 1996.
4. Montgomery SA, Henry J, McDonald G, Dinan T, Lader M, Hindmarsh I, Clare A, Nutt D. Selective serotonin reuptake inhibitors: meta-analysis of discontinuation rates. *Int. Clin. Psychopharmacol.* 1993; **9**: 47–53.
5. Woods SW and Baker JA. Cost-effectiveness of antidepressant treatment reassessed. *Br. J. Psychiatry*, 1997; **170**: 257–263.
6. Simon GE, Von Korff M, Heligenstein JH *et al.* Initial antidepressant

- choice in primary care: effectiveness and cost of fluoxetine vs TCAs. *J. Am. Med. Assoc.*, 1996; **275**: 1897–1902.
7. Department of Health. (1994) *Guidelines for the Economic Evaluation of Pharmaceuticals*, press release 94/251, Department of Health, London.
 8. Siegel JE, Torrance GW, Russell LB, Luce BR, Weinstein MC, Gold MR. Guidelines for pharmacoeconomic studies. *Pharmacoeconomics*, 1997; **11**(2): 159–168.
 9. Johannesson, M. Economic evaluation of drugs and its potential uses in policy making. *Pharmacoeconomics* 1995; **8**(3): 190–198.
 10. Hotopf M, Lewis G and Normand C. Are SSRIs a cost-effective alternative to tricyclics? *Br. J. Psychiatry*, 1996; **168**: 404–409.
 11. Song F, Freemantle N, Sheldon TA, House A, Watson P, Long A, Mason J. Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *Br. Med. J.* 1993; **306**: 683–687.
 12. Freemantle N, Long A, Mason J, Sheldon T, Song F, Watson P, Wilson C. The treatment of depression in primary care. *Effective Health Care* 1993; Bulletin No. 5.
 13. Zammit-Lucia J, Dasgupta R. Reference pricing: the European experience. St Mary's Hospital Medical School, Health Policy Unit, Health Policy Review Paper No. 10, 1995.
 14. Hutton J, Borowitz M, Olesky I, Luce BR. The pharmaceutical industry and health reform: lessons from Europe. *Health Affairs* 1994; Summer, 98–111.
 15. Davis R, Wilde MI. Sertraline: A pharmacoeconomic evaluation of its use in depression. *Pharmacoeconomics* 1996; **10**(4): 409–431.
 16. Gray AM, Marshall M, Lockwood A, Morris J. *Br. J. Psychiatry* 1997; **170**: 47–52.
 17. Bisslerbe JC, Boyer P, Souetre E *et al.* Poster Presentation, CINP, 1996.
 18. Sintonen H, Lonnqvist J, Kiviruusu O. Cost-effectiveness/utility analysis of two drug regimens in the treatment of depression. National Centre for Health Program Evaluation, Melbourne, Working Paper 37, 1994
 19. Stewart A. Choosing an antidepressant: effectiveness based pharmacoeconomics. *J. Affective Disorders*, in press, 1998.
 20. Forder J, Kavanagh S, Fenyo A. A comparison of the cost-effectiveness of sertraline versus tricyclic antidepressants in primary care. *J. Affective Disorders* 1996; **38**: 97–111.
 21. Thompson C. Management of depression in real-life settings: knowledge gained from large-scale clinical trials. *Int. Clin. Psychopharmacol.* 1994; **9**(suppl. 3): 21–25.
 22. Sclar DA, Robison LM, Skaer TL, Galin RS, Legg RF, Nemecek NL *et al.* Antidepressant pharmacotherapy: economic outcomes in a health maintenance organization. *Clin Therapeut.* 1994; **16**(4): 715–730.
 23. Sclar DA, Robison LM, Skaer TL, Galin RS, Legg RF, Nemecek NL *et al.* Antidepressant pharmacotherapy: Economic evaluation of fluoxetine, paroxetine and sertraline in a health maintenance organization. *The Journal of International Medical Research*, 1995; **23**: 395–412.
 24. Skaer TL, Sclar DA, Robison LM, Galin RS, Legg RF, Nemecek NL. Economic evaluation of amitriptyline, desipramine, nortriptyline and sertraline in the management of patients with depression. *Curr. Therapeut. Res.* 1995; **56**(6): 556–567.
 25. Thornton JG, Lilford RJ, Johnson N. Decision analysis in medicine. *Br. Med. J.* 1992; **304**: 1099–1103.
 26. Stewart A. Decision analysis and mental health evaluations. In: Knapp M, ed. *The Economic Evaluation of Mental Health Care*, 1995, Arena, Aldershot, 207–214.
 27. Glick H, Kinoshian B, Schulman K. Decision analytic modelling: some uses in the evaluation of new pharmaceuticals, *Drug Information J.* 1994; **28**: 691–707.
 28. Sheldon T. Problems of using modelling in the economic evaluation of health care. *Health Econ.* 1996; **5**: 1–11.
 29. Le Pen C, Levy E, Ravily V, Beuzen JN, Meurgey F. The cost of treatment dropout in depression—a cost-benefit-analysis of fluoxetine vs tricyclics. *J. Affective Disorders* 1994; **31**: 1–18.
 30. Nuijten MJC, Hardens M, Souetre E. A Markov-process analysis comparing the cost-effectiveness of maintenance therapy with citalopram with standard therapy in major depression. *Pharmacoeconomics* 1995; **8**(2): 159–168.
 31. Jonsson B and Bebbington PE. What price depression? The cost of depression and the cost-effectiveness of pharmacological treatment. *Br. J. Psychiatry* 1994; **164**: 665–673.
 32. Dunbar GC, Cohn JB, Fabre LF, Feighner JP, Fieve RR, Mendels J, Shrivastava RK. A comparison of paroxetine, imipramine and placebo in depressed outpatients. *Br. J. Psychiatry* 1991; **159**: 394–398.
 33. Hatzidandreu EJ, Brown RE, Revicki DA, Turner R, Martindale JJ, Levine S, Siegel JE. Cost-utility of maintenance treatment of recurrent depression with sertraline versus episodic treatment with dothiepin. *Pharmacoeconomics* 1994; **5**: 249–264.
 34. Sonneberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med. Decision Making* 1993; **13**: 322–338.
 35. Stewart A. Antidepressant pharmacotherapy: cost comparison of SSRIs and TCAs. *Br. J. Med. Econ.* 1994; **7**: 67–79.
 36. Old Age Depression Interest Group. How long should the elderly take antidepressants? A double-blind placebo-controlled study of continuation/prophylaxis therapy. *Br. J. Psychiatry* 1993; **162**: 175–182.
 37. Thase ME. Long-term treatment of recurrent depressive disorders. *J. Clin. Psychiatry* 1992; **53**(suppl.): 32–44.
 38. Kind P, Sorensen J. Modelling the cost-effectiveness of the prophylactic use of SSRIs in the treatment of depression. *Int. Clin. Psychopharmacol.* 1995; **10**(suppl. 1): 41–48.
 39. Montgomery SA, Brown RE, Clark M. (1996) Economic analysis of treating depression with nefazodone v. imipramine. *Br. J. Psychiatry* 1996; **168**: 768–771.
 40. Donoghue JM, Tylee A. The treatment of depression: prescribing patterns of antidepressants in primary care in the UK. *Br. J. Psychiatry* 1996; **168**: 164–168.