

# Which antidepressant? A commentary from general practice on evidence-based medicine and health economics

D P KERNICK

## SUMMARY

**Background.** With increasing demand for health care, evidence-based medicine combined with health economics offers a method of optimizing allocation of limited resources. Depression is an illness that has a high prevalence with important medical, social and economic implications. More than 90% of depression is diagnosed and treated in general practice.

**Aim.** To review the effectiveness of an evidence-based approach combined with health economics in deciding whether a tricyclic antidepressant (TCA) or a selective serotonin reuptake inhibitor (SSRI) should be used in the treatment of depression in general practice.

**Method.** An evidence-based strategy tested the two treatments against the criteria of appropriateness, efficacy, effectiveness and value for money.

**Results.** Although both drugs were equally efficacious, their relative effectiveness and value for money could not be accurately defined.

**Conclusion.** An evidence-based approach does not make clear whether SSRIs or TCAs should be used for the treatment of depression in general practice. Research questions arising from general practice should be addressed in a relevant setting and should yield answers that will complement and support a more pragmatic system of medicine rather than seek to direct it.

**Keywords:** antidepressive agents; health service economics; evidence-based medicine.

## Introduction

WITH increasing demands on limited health care resources, evidence-based medicine seeks to direct interventions into areas of proven effectiveness,<sup>1</sup> and health economics assists in the difficult task of determining how best to use such interventions. Although other approaches are effective in the treatment of depression,<sup>2</sup> pharmacological intervention remains the treatment of choice in primary care.<sup>3</sup> SSRIs were introduced in the late 1980s and now account for 23% of the volume and 63% of the costs of antidepressant prescribing in general practice.<sup>4</sup> Whether the advantages claimed for these drugs are commensurate with their additional costs is an important question for the general practitioner (GP).

## Method

An evidence-based strategy converts needs into a specific question and puts critically appraised evidence into practise. The effectiveness of this model was tested by applying the four criteria below to the question, 'Should depression be treated in primary care and, if so, with which drug treatment?'

- Appropriateness: Should the illness be treated?
- Efficacy: Which intervention is validated under experimental conditions?
- Effectiveness: Which efficacious interventions are effective in their intended setting?
- Value for money: Which effective interventions are worth paying for?

Articles for inclusion were obtained from a search of Medline using the terms TCA, SSRI, and economics/depression/general practice; further references were then obtained from the articles found.

## Results

### *Is it appropriate to treat depression?*

The most basic level of health choice is a societal decision whether to use resources to treat a particular condition. *The Health of the Nation* report has identified mental illness as a key area.<sup>5</sup> The prevalence of major depression is around 5%; some 13% of patients presenting to GPs for a new illness will have a depressive disorder, and of these 50% will go unrecognized at the initial contact.<sup>3</sup> It has been estimated that up to 20% of new somatic presentations and 3% of consecutive attenders may have an underlying depressive illness.<sup>6</sup> Estimates of the direct costs of depressive illness are between £222 million<sup>7</sup> and £420 million a year,<sup>8</sup> and indirect costs may exceed £3 billion a year.<sup>8</sup> Clearly, it is appropriate to treat depression.

### *Are the treatment options efficacious?*

More than 90% of trials reviewed were undertaken in a hospital setting, where certain features of depression predict the response to antidepressant medication and form the basis of the DSM IV diagnosis of major depression.<sup>9</sup> Song undertook a meta-analysis of 64 randomized control trials comparing SSRIs and TCAs and concluded that there was no difference in efficacy between the two groups,<sup>10</sup> a finding confirmed by Anderson in a similar study of 55 controlled trials.<sup>11</sup> In a meta-analysis of drop out rates, Anderson estimated that the risk of patients stopping treatment was 10% lower with SSRIs than with TCAs.<sup>12</sup> Montgomery found that significantly fewer patients discontinued treatment when taking SSRIs (14.9%) compared with those taking TCAs (19%)<sup>13</sup> — findings that were confirmed by a more recent systematic review by Hotopf.<sup>14</sup> These studies show equal clinical efficacy for both drugs but with a slightly higher drop out rate for TCAs.

### *Are the treatment options effective?*

Depression can be treated effectively in general practice;<sup>3</sup> 90% of cases are treated in this setting without consultant referral<sup>15</sup> and the additional costs of specialist treatment do not yield clinical benefit.<sup>16</sup> Published studies treat patients with therapeutic doses who satisfy criteria for major depression. In general practice, therapeutic doses of TCAs are rarely achieved<sup>17</sup> whereas more than 80% of prescriptions for SSRIs are issued at a therapeutic dose at the initial consultation.<sup>18</sup> In practice, patients are more likely to receive an adequate therapeutic dose of an SSRI

D P Kernick, BSc, MRCP, general practitioner, Exeter.  
Submitted: 21 May 1996; accepted: 2 October 1996.

© British Journal of General Practice, 1997, 47, 95-98.

and a dose of a TCA that is unlikely to give side-effects but that may not reach therapeutic levels.

To prevent relapse, a four- to six-month continuation phase is recommended after recovery.<sup>3,19</sup> However, the average length of published trials was six weeks, with three trials at eight weeks and one trial at 12 weeks. These studies describe only the response to an antidepressant and give no information on the remission or recovery from the illness over a time-span more relevant to primary care.

Egger has outlined some of the problems with meta-analysis.<sup>20</sup> The perspectives obtained from these systematic reviews may not be altogether appropriate when applied to the unique circumstances of individual patients: other untested outcomes, such as quality of life, may be equally relevant. Recently a comparative randomized prospective trial has reported from a primary care setting in the United States (US) over a period of six months; its authors conclude that clinical and quality of life outcomes provide no clear guidance on initial selection of antidepressant and suggest that patients and physician preferences are the appropriate basis for selection.<sup>21</sup> Although clinical trials have shown that SSRIs and TCAs are equally efficacious, their relative effectiveness in general practice is still unclear.

#### *Which treatment of depression is worth paying for?*

Health economics relates the cost of effective interventions to their benefits, thereby helping doctors to make choices when resources are limited. Ideally, economic analysis and evaluation should be conducted in parallel with clinical trials,<sup>22</sup> but in a systematic review Hotopf<sup>14</sup> found no concurrent economic analyses and suggested that methodological problems may preclude this approach. However, a more recent US trial found no overall difference in direct costs after six months.<sup>21</sup> In any economic analysis, problems arise with the allocation of monetary values to direct and indirect costs, and with the perspective from which the economic analysis should be taken.

**Problems with direct costs.** As comprehensive direct costs are not available, decision-analytic models have been used to compare alternative treatments by combining available data into a decision tree, where the consequences of different treatments can be described in a finite set of discrete events with well-defined probabilities. Where data is not available, expert opinions are sought on likely outcomes, and similar costs are derived for SSRIs and TCAs.<sup>7,23</sup> However, the assumptions made in this technique may not reflect the decision process in practice.

**Problems with indirect costs.** The indirect costs of depression are far harder to evaluate but are likely to be more significant. They are:

- Loss of productivity
- Suicide and parasuicide, and
- Behavioural toxicity.

**Loss of productivity.** This may represent a substantial proportion of the indirect costs of depression. Difficulties arise in this area as the contribution to overall economic activity will be a function of a person's level of responsibility and of the type of remuneration received. Beuzen undertook a cross-sectional study of patients being treated for depression and found that the risk of work loss was significantly lower with SSRIs than with other treatments.<sup>24</sup> Additional costs to the economy will be incurred by carers and social support systems.

**Suicide and parasuicide.** Although 54% of people presenting with deliberate self-harm are depressed,<sup>25</sup> the exact relationship between suicide and depression is unknown. The most pronounced difference between SSRIs and TCAs is their relative toxicity in overdose; Henry<sup>26</sup> found a death rate per million pre-

scriptions of 34 for TCAs compared with 2 for SSRIs. Isacson screened blood samples of 3400 victims of suicide and suggested that therapeutic failure may be a greater problem than toxicity, concluding that few people were taking antidepressants at the time of suicide.<sup>27</sup> Jick analysed the general practice records of 143 people who committed suicide and found that overdose with antidepressants accounted for only 14% of the suicides.<sup>28</sup>

Only small numbers of patients kill themselves through toxic concentrations of antidepressants, and suicidal patients who are prescribed a non-toxic drug may seek alternative methods of killing themselves. Freemantle concluded that the cost of a strategy to reduce suicide by changing to SSRIs for routine first-line use would be unnecessarily high.<sup>29</sup> Since relative mortality data is not from randomized trials it may reflect differences in prescribing patterns for patients felt to be at risk of committing suicide. These studies have provoked unresolved controversy over the relationship between toxicity and mortality in cases of overdose.

The incidence of parasuicide is between 10 and 20 times higher than that of suicide, with potential costs to the National Health Service (NHS) of more than £50 million.<sup>30,31</sup> It is likely that overdoses from SSRIs will require less intensive treatment and shorter hospitalization, but unfortunately there is no data in this area.

**Behavioural toxicity.** There are significant differences between SSRIs and TCAs in their effects on psychomotor performance and cognitive function; in both cases, the effects are exacerbated by small amounts of alcohol.<sup>32</sup> The importance of behavioural toxicity is becoming increasingly recognized, and with widespread car ownership there may be important implications for compliance. A recent commentary suggested that 10% of all traffic casualties were taking psychotropic medication that may have contributed to the accident,<sup>33</sup> while other authors have emphasized accidents at work and at home, particularly in the elderly.<sup>34</sup> However, a recent review concluded that there were insufficient epidemiological data to indicate the extent to which antidepressants contribute to accidents.<sup>35</sup>

#### *The problem of perspective*

The perspective of an economic analysis must be defined since it dictates which costs should be counted. Different answers may be obtained from the perspectives of the individual patient, the GP fundholder, the purchasing authority, the NHS and society in general. Adopting the societal approach often involves valuing items (such as suicide) that have ambiguous costs and have no financial relevance for other stakeholders. The perspective of an economic analysis should reflect the content of the study. GPs may find it difficult to reconcile societal perspectives with the pressure to contain practice prescribing budgets within the restricted financial environment in which they operate. On the basis of available data, the economic implications of the treatment options studied remain unresolved.

### **Discussion**

In 1972, Cochrane argued for a closer integration between medicine and the scientific method based on a wider use of randomized control trials;<sup>36</sup> more recently, the importance of economic analysis alongside clinical trials has been emphasized.<sup>22</sup> This commentary has outlined three areas of this debate relevant to primary care.

#### *Obtaining the evidence*

An evidence-based approach has been tested by its application to

a simple question and has been found wanting. This result may reflect a limitation of this mechanism — the integration of large numbers of piecemeal trials that generalize poorly to the setting where the intervention takes place.

In a critical perspective of the meta-analysis, Thompson concluded that this technique does not provide definite answers to complex problems and recommended caution in their interpretation.<sup>37</sup> Asch has outlined the difficulties of extrapolating population perspectives to predict the outcomes of individuals — particularly in the community setting, where patients receive treatment in the context of a special doctor–patient relationship with physical, psychological, social and cultural dimensions.<sup>38</sup>

The ideal strategy would be to randomize SSRIs and TCAs in general practice and to collect primary and secondary clinical and economic data prospectively, over a period of at least a year. This approach is likely to be more rewarding than 10 years of research effort that has yet to answer a simple question. Although a trial that satisfies some of the criteria has recently been reported from the US,<sup>21</sup> such studies are costly to organize and unlikely to be applied to many interventions.

### Problems with health economics

Health economics is a complex discipline, and its framework of often arbitrary constructs may limit both its accessibility and its acceptability to providers and purchasers. The large indirect cost implications of the two drugs can only be estimated, while input costs vary widely across the NHS, and most issues relating to the statistical analysis of economic data remain unresolved.<sup>39</sup>

The difficulties of integrating economics with healthcare, particularly in the field of depression, are well recognized.<sup>40</sup> The GP is also confronted with a dilemma over which economic perspective to adopt, as the financial directives of his environment may not coincide with the societal viewpoint. It is unlikely that the cost implications of the drugs studied will be resolved over their therapeutic life-span.

### Using evidence-based medicine in general practice

Medical research has had little effect on the delivery of primary care, which still relies to a large extent on individual experience, opinion and invalidated treatment.<sup>41</sup> Poor presentation of guidelines has been cited as the main reason for lack of research implementation,<sup>42,43</sup> but there may be more fundamental reasons for this observation.

Hammond described a cognitive continuum of decision making whereby structured systems can be examined by a highly analytical approach;<sup>44</sup> but, as tasks become less organized, intuition predominates, with decisions based on past experience, future expectations and complex human interrelationships. In 1984, Howie emphasized the essential relationship between information, knowledge and wisdom in medicine,<sup>45</sup> a call reiterated more recently by McCormick.<sup>46</sup> Cochrane's postulates<sup>36</sup> may be relevant for the secondary care sector (where outcomes do not reflect the complex interactions between the many elements of health), but in general practice there are other pathways to sound clinical judgement, and decisions are based on a number of factors, which may include evidence-based medicine and health economics.

Since the introduction of SSRIs, GPs, on average, may have treated more than 300 patients with depression, some with TCAs and some with SSRIs. Over the years GPs will have built up a picture of the perceived effectiveness of each class of drug in their own patients and in their particular setting. Their impressions will have no basis in statistics but will offer a unique decision making resource, which may be superior to an evidence-based approach using existing research. The scientific method of evidence-based medicine dictates a rigorous approach and an

optimization of outcomes of cost, effectiveness and utility that are rarely possible in general practice. A pragmatic approach accepts a degree of uncertainty and inconsistency and seeks to maximize the rational, eradicate the irrational, and live with the non-rational.

### Conclusion

Although SSRIs and TCAs are equally effective over short periods in secondary care, an evidence-based approach has failed to define clearly their relative effectiveness or value for money in general practice. In order to gain credibility, trial designs need to be relevant to the setting in which the intervention is delivered, cognizant of other inputs such as knowledge, experience and intuition, and ready to draw on other disciplines such as sociology, psychology, communication and decision theory. Research in primary care should answer questions that will complement and support a more pragmatic system of health delivery rather than seek to direct it. It may be that GPs know something that Cochrane did not about the subservience of scientific evidence to wisdom?

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### Acknowledgement

The author's practice receives research funding from the NHS Executive South and West Research and Development Directorate.

### Address for correspondence

Dr D P Kernick, The St Thomas Medical Group, Cowick Street, Exeter EX4 1HJ.