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Conclusion

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Antidepressants, as the term is currently understood, were introduced into clinical practice in the late 1950s. The first of these was imipramine, shortly to be followed by amitriptyline and then by a series of related compounds – all chemically 'tricyclics'. These subsequently became known as the 'first-generation' antidepressants; imipramine and amitriptyline in particular have since become the standards against which others have been compared.

About the same time, the first generation of monoamine oxidase inhibitors was also being introduced. The clinical effects of both groups of compounds were essentially serendipitous discoveries, and for more than 30 years there has been a continuous search for antidepressants that would be more effective and better tolerated. Although many such drugs have been introduced into clinical practice, there is so far no evidence that any of them are more effective than the original tricyclics, or that any one has a more rapid onset of effect than any other. In these two respects, 30 years of research and development have achieved relatively little.

However, there are two attributes of antidepressants that have great clinical importance – their side-effect profile and, because of the risk of suicide in depression, their toxicity in overdose. In respect of these considerations, considerable progress has in fact been made.

The process of development has proceeded through the 'second-generation' antidepressants, a group of chemically unrelated compounds, to the selective serotonin reuptake inhibitors (SSRIs). In addition, a new class of reversible mono-oxidase inhibitors (RIMAs) has been developed, and these lack most of the undesirable effects of their forebears.

In the search for new antidepressants, though, many compounds fail to meet the high standards of safety and efficacy now required. For every new drug that reaches the clinic, a very large number will have failed to clear one or other hurdle along the way; in consequence, new drugs are increasingly more expensive to produce. The emphasis on high standards of research and development has partly been a response to pressures from society, mediated through government, and has resulted in increasingly more stringent and complex regulatory and registration requirements.

More recently, a new classification of antidepressants has emerged, having two categories – cheap and expensive – with the result that a contradictory situation has arisen. On the one hand, society constantly demands better and safer drugs, which are increasingly more expensive to produce. On the other hand, this same society is saying that because of its inability to meet the increasing demands for health care, it can no longer afford to pay for them.

The last 25 years have also seen significant changes in the regulatory process. Early concerns were almost entirely with safety, leading to the establishment in the UK, first of the Dunlop Committee and eventually of the Committee on the Safety of Medicines. Subsequently, emphasis was placed not only on safety but also on efficacy, and now it seems that 'need' is increasingly becoming a concern. Not only is it necessary to demonstrate that a drug is safe and efficacious, but also that society really needs it. Obviously, this requirement does not apply to major breakthroughs, but rather to purported marginal improvements and particularly to drugs somewhat derisively called 'me-toos'.

Regulations are now being drafted in some countries which require, perhaps not for the licensing of a new drug, but certainly for its reimbursement through the health-care system, evidence from an additional type of study which will establish the need for it. Both the medical community and the pharmaceutical industry will be invited to consider what type of study design would be most appropriate for this, but it seems likely that the cost–utility approach will prove to be the most acceptable. In the design of such a study, it is necessary not only to consider a drug's direct and indirect costs, but also its effect on intangibles; this immediately raises the issue of the effect of drugs on quality of life, and how this should be assessed. All over the world, there are growing concerns that demands for medical care are outstripping the ability to provide them. Inevitably, this means that it may be necessary to set priorities and to concede reluctantly that the treatment of some disorders must take precedence over that of others.

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Society is perhaps beginning to recognise the importance of depression as a major public health concern. The Depression Awareness Recognition and Treatment programme in the USA, sponsored by the National Institute for Mental Health, and the Defeat Depression Campaign in the UK have both drawn attention to this, suggesting that depression is deserving of a high place on any list of priorities. It has been reported that as many as 13% of patients seen in general practice have major depressive disorder (Bridges & Goldberg, 1987).

However, from the standpoint of health economics, two questions need to be asked about depression: what is the cost of the illness itself, and what is the cost of its treatment? Surprisingly, very few studies up to now have considered either of these questions.

The results of a study in the USA (Stoudemire *et al*, 1986) suggested that if both direct and indirect costs were included, as well as the cost to the nation of people committing suicide (admittedly a contentious subject), the total cost of depression per annum was $16.3 billion. In the UK, Kind & Sorensen (1993) estimated the direct costs to be £411 million and the indirect costs £2814 million, but in this study the cost of suicide was excluded. In relations to such totals, the relative cost of antidepressants appears to be small: in Kind's study, this accounted for less than 10% of direct costs. It could be questioned, therefore, why authorities show so much preoccupation with the cost of antidepressant drugs when it might be more appropriate to attempt to make inroads into the other 90% of costs or the total cost of the illness. This appears to represent a preoccupation with cost-minimisation, which would be a short-sighted policy.

As suggested above, progress in the development of better antidepressants has been achieved mainly in the areas of side-effect profile and toxicity in overdose. However, this needs to be translated not only into clinical benefits, but also into cost saving. What, for example, are the economic benefits of reduced cardiotoxicity or improvements in dental hygiene (Bertram, 1984) due to lack of anticholinergic side-effects? In the narrower context of direct costs, anticholinergic side-effects may be expected to influence compliance, and in the broader context of cost–utility, they may impair quality of life. Some antidepressants that are unduly sedative cause cognitive and psychomotor impairment, at least in the early stages of treatment. It is possible that this could contribute to more accidents and injuries on the road, and if that were so, should the costs of these not be considered when assessing the cost of the drug?

From the economic point of view, toxicity of antidepressants in overdose and the economic costs of suicide have been vexed issues. Does suicide cost money or does it save money? Should the attitude of the transport economist be taken, in which the value of a human life is placed as high as £500 000 and should this figure be added to the cost of older, toxic antidepressants for every successful overdose? Alternatively, does the fact that people who kill themselves no longer require services and benefits mean that expense is spared? However, not every attempted suicide succeeds, and the costs of caring for patients who take overdoses with toxic antidepressants is considerable; this too must be included in any equation.

So far as the evaluation of treatment is concerned, there seems to be a need to move into new areas, and to devise new types of study and new methodologies. In health economic assessments, the conventional clinical trial will no longer be sufficient to meet all our requirements. Clinical trials are usually of short duration, include highly selected patients, and do not regularly provide long-term data. More information is required about the natural history of the disorder and such features as chronicity and relapse. Nevertheless, using data derived from clinical trials (Jonsson & Bebbington, 1993), it has been claimed that when withdrawal from and compliance with treatment are considered, the use of a new SSRI is no more expensive than the use of an older tricyclic, despite higher unit costs. However, there is a need for a new kind of study, of a more naturalistic type, to provide the type of information required for valid economic evaluation. In such an investigation, which might be termed a 'drug utilisation study', patients prescribed an antidepressant according to selection procedures which apply in everyday clinical practice could be identified and then followed through all eventualities, for as long as necessary. Cohorts of patients who had had different treatment methods prescribed for them – whether antidepressant or otherwise – could then be compared.

It has to be recognised that the general public does not appear to have great confidence in the efficacy of antidepressants. In the MORI poll commissioned by the Royal College of Psychiatrists for the launch of its Defeat Depression Campaign, only 48% of those questioned thought that antidepressants work. Almost 80% considered counselling to be the best treatment.

If cost–utility studies are to be performed in the future, an essential prerequisite will be the ability to measure sensitively 'intangible' effects, particularly those which alter the quality of life. However, the types of measure at present available, designed for other specific purposes, are unlikely to prove entirely suitable when applied to depression and its treatment.

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Different types of measurement will need to be developed.

It is also possible that the use of some antidepressants, like other drugs, might in the future carry certain legal implications. Could a doctor be challenged for prescribing an antidepressant that was toxic in overdose, for a patient who subsequently uses it to commit suicide, when a safer substance could have been given instead?

We may be approaching a time when informed consent will become a necessity: patients would then need to be informed about dangers of overdose before being asked to take a particular drug.

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