Selective serotonin reuptake inhibitors

Drugs related to tricyclic antidepressants are a mixed bag

EDITOR,—N Freemantle and colleagues propose that, compared with selective serotonin reuptake inhibitors, "newer tricyclic and related antidepressants . . . will have similar impact on rates of suicide but at considerably less cost."¹ The drugs that are listed as newer tricyclic and related antidepressants, however, have important differences in pharmacology, clinical profile, toxicity, and cost.

Maprotiline is indeed related to tricyclic antidepressants both structurally and pharmacologically. It is also equally toxic,² as table 1 of the authors' article clearly shows. To class it among compounds that are of "similar toxicity" to selective serotonin reuptake inhibitors is misleading and a serious error. Trazodone and mianserin are relatively safe in overdose but differ from selective serotonin reuptake inhibitors in being highly sedating.³ For some patients a sedating drug will be preferred,³ but this will be a clinical decision rather than an economic one. Economic factors may, of course, favour the use of one "safe" sedating antidepressant over another. Trazodone is as expensive as selective serotonin reuptake inhibitors, and, although mianserin is cheaper, the expense and inconvenience of the blood count monitoring required by the *British National Formulary* have not been taken into account in the costs shown by the authors.

Viloxazine is used little in Britain. It was released on to the market before licensing authorities required new antidepressant drugs to undergo rigorous placebo controlled testing of efficacy. Its efficacy compared with that of placebo has not been satisfactorily shown,⁴ and calls for its more widespread prescription require careful examination.

Lofepramine is non-sedating and relatively safe in overdose. It is indeed a viable alternative to the selective serotonin reuptake inhibitors in the treatment of major depression.⁵ Evidence suggests that it is more effective than placebo,⁵ but not at the dose that Freemantle and colleagues used to calculate the cost of treatment in table II of their article. The dose of lofepramine recommended in the *British National Formulary* is 140-210 mg daily; in relation to the doses of the selective serotonin reuptake inhibitors, trazodone, and mianserin given in table II the therapeutic equivalent for

lofepramine is probably 210 mg. At this dose the cost-benefit of lofepramine over selective serotonin reuptake inhibitors is diminished.

Although the *British National Formulary* uses the classification "tricyclic and related antidepressant drugs," these drugs cannot be unthinkingly lumped together. Presenting a "weighted average" of such disparate elements in terms of toxicity and cost conveys no useful information. Freemantle and colleagues raise important questions, but their article shows that those who study the health economics of the prescribing of antidepressant drugs need to have some knowledge of psychopharmacology. If they do not they will promulgate therapeutic recommendations that are at best clinically naive and at worst (as in the misclassification of maprotiline) a potential hazard.

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Tricyclics are less safe

EDITOR,—The article by N Freemantle and colleagues, advocating the use of new tricyclic antidepressants and related drugs in preference to the selective serotonin reuptake inhibitors to prevent suicide, is disturbing.¹ The statement that the newer tricyclic antidepressants and related drugs are of similar toxicity to the selective serotonin reuptake inhibitors is false. To suggest that the risk of death from mianserin in overdose is comparable to that associated with the selective serotonin reuptake inhibitors and to ignore the cost of blood monitoring, which the use of mianserin necessitates, shows a lack of understanding of the wider issues. Likewise, to encourage the prescribing of maprotiline, which has been shown to provoke attempts at suicide, is dangerous.²

In their analysis of cost the authors used the World Health Organisation's tables of defined daily doses. The recognised effective dose of lofepramine is 210 mg a day, which results in a monthly cost of £15.40, compared with a monthly cost of fluoxetine 20 mg a day of £20.³ While I agree that newer tricyclic antidepressants and related

drugs are as efficacious as the selective serotonin reuptake inhibitors in treating the acute phase of depression, evidence of their efficacy in preventing relapse and recurrence of depression is lacking. In contrast, there are good data on the efficacy of the selective serotonin reuptake inhibitors in the long term treatment of depression. This issue cannot be ignored when the cost of preventing suicide is being considered.

It is easy to equate the treatment of depression with the prevention of suicide, but many more factors are involved in preventing suicide. If we continue to have high levels of prescribing of antidepressants in the community, for whatever disorder, we should ensure that the drugs prescribed are the safest available. I believe that the selective serotonin reuptake inhibitors are the safest drugs available, and to discourage their use on the basis of the false assumptions made in Freemantle and colleagues' article is both short sighted and dangerous.

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Calculation of costs is incorrect

EDITOR,—We are concerned that N Freemantle and colleagues—a group funded by the Department of Health—have again published a flawed and inaccurate study that is seriously misleading.¹ By focusing on drug costs to the exclusion of all other direct and indirect costs they have failed to follow the guidance on good practice in the conduct of economic evaluations of medicines issued this year by the Department of Health and Association of the British Pharmaceutical Industry² and other guidelines on economic evaluation.³

The direct costs of attempted suicide are sizeable. Preliminary data from a prospective study in the United States of 207 overdoses of different antidepressants suggest that total acute medical costs are four times lower for overdoses of fluoxetine than for overdoses of tricyclic antidepressants (D Revicki, personal communication). In addition, indirect costs such as loss of earnings considerably increase the total burden of suicide. The Department of Transport in Britain values a life at £744 060 (June 1993 price).⁴ This includes loss of earnings; the cost of transport by ambulance and hospital treatment; and the cost of the pain, grief, and suffering to relatives and friends. This is double the cost of saving a life (£370 000) that Freemantle and colleagues estimate would result if selective serotonin reuptake inhibitors totally replaced tricyclic antidepressants.

Freemantle and colleagues also quote selectively from the literature and do not include in their calculations the 35% reduction in the price of fluoxetine in January 1993. To support their assertion that selective serotonin reuptake inhibitors are neither more effective nor better

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tolerated than tricyclic antidepressants they rely on their own meta-analysis, which created a storm of critical correspondence in the *BMJ*. They neglect to discuss a more recent meta-analysis, which concluded that a significantly higher proportion of patients taking tricyclic antidepressants (341/2296 (14.9%)) than of patients taking selective serotonin reuptake inhibitors stop treatment because of side effects ($P < 0.01$).³ This has important implications for comparisons of the overall direct costs of prescribing tricyclic antidepressants and selective serotonin reuptake inhibitors.

The *Health of the Nation* objective to reduce the rate of suicide deserves support. The use of selective serotonin reuptake inhibitors to treat depressed people is a tangible and effective way of reducing the number of successful suicides by several hundred each year. Moreover, the personal tragedy that any suicide brings to the family, friends, and doctors of the victim cannot be ignored.

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Hidden costs ignored

EDITOR,—N Freemantle and colleagues conclude that a change to prescribing selective serotonin reuptake inhibitors as routine first line antidepressants would be ill advised on the grounds of financial cost.¹ They conclude this despite taking into account the cost of suicides associated with use of tricyclic antidepressants.

Death from overdose is only one way in which a depressed patient can die because of tricyclic antidepressants. When the relative benefits of a change in prescribing policy are assessed other, hidden costs must be included in the calculations. There is ample evidence that the older tricyclic antidepressants, and some of the newer agents, impair cognitive and psychomotor function. Laboratory investigations have shown that amitriptyline and dothiepin slow the speed of reaction equivalent to a car's length in the stopping distance at a speed of 113 km/h (70 mph).² This is in considerable contrast to those selective serotonin reuptake inhibitors that have been tested. A recent commentary suggested that a tenth of casualties in road traffic accidents were taking psychotropic drugs that may have contributed to the accident.³ Epidemiological studies provide further evidence for the causal role of psychotropic drugs in road traffic accidents. Specifically, Ray *et al* showed that patients taking amitriptyline 125 mg a day (or the equivalent dose of other tricyclic antidepressants) are six times more likely to be involved in road traffic accidents than patients taking other drugs.⁴

The cost of a fatal road traffic accident is on average £762 840 (1991 figures).⁵ Those accidents due directly to tricyclic antidepressants must be accounted for if accurate pharmacoeconomics is to be used to guide prescribing practice. Costs also arise from other side effects of tricyclic antidepressants—postural hypotension leading to falls, for example. The main difference between tricyclic

antidepressants and selective serotonin reuptake inhibitors is not cost but safety in clinical use. The policy of promoting "cheap" but toxic drugs does nothing to improve safety on the roads, in the home, or in the workplace.

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Total profile of drug should be considered

EDITOR,—N Freemantle and colleagues seem to have accepted that greater use of selective serotonin reuptake inhibitors would probably result in a reduction in the number of suicides, but they have rejected use of those drugs as first line treatment because the cost of the lives saved would be excessive.¹ It would perhaps be surprising if an economic case could have been made for first line use of selective serotonin reuptake inhibitors solely on the basis of a reduced number of suicides. Looking at suicides alone provides an incomplete picture—for example, it has been shown that use of tricyclic antidepressants may be associated with road traffic accidents² and, in elderly people, with an increase in hip fractures.³ The potential benefits of selective serotonin reuptake inhibitors and the wide policy implications of their use should be related to their total profiles, not to a single aspect taken in isolation.

Even within the limited context of suicide, however, the authors' analysis must be considered to be partial. The authors concede two major omissions from their calculations. Firstly, on the basis of their own, putatively flawed,² previous meta-analysis⁴ they assumed that there is no difference between drug classes in terms of compliance and therefore the cost of drop outs. A meta-analysis by Montgomery *et al* provides evidence that tricyclic antidepressants are less well tolerated than other drugs.⁵ Improved compliance could result in a reduction in suicides overall, not just those related to antidepressant toxicity.

Secondly, the authors only briefly refer to the costs of treating attempts at self poisoning, which are likely to be lower with the selective serotonin reuptake inhibitors. Here the problem is again the lack of data on which to base calculations. Lack of data does not mean that an important element of cost can be ignored; it highlights the limitations of the study and of the conclusions that can be drawn from it.

Finally, the authors finished their paper with a "burning fuse." What will happen when a doctor who has been advised on grounds of cost to prescribe cheap but toxic antidepressants is confronted by the family of a patient who has used them to commit suicide?

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Unsuccessful treatment may be related to non-response or non-compliance

EDITOR,—Equating prevented suicides with savings in the cost of antidepressants is a novel way of expressing budgetary savings achievable by changes in prescribing strategy. N Freemantle and colleagues' approach, however, considers only the direct costs of drugs to the health service and rests on the major assumption that all drugs are associated with 100% compliance.¹ While equal efficacy is generally accepted, equal compliance in the natural setting remains unproved; data on drop out rates in clinical trials do not properly address this issue.² In addition, suicide associated with unsuccessful treatment of depression may be related to non-response or non-compliance. Non-response may be related to dose. Underdosing with older tricyclic drugs is widespread.³ Non-compliance relates largely to side effects. A marginal difference in the profiles of side effects, which might be tolerable in the short term, could be more important if treatment is continued for up to five years.⁴ Also, the emergence of substantial suicidal ideation has been shown to be significantly lower for fluoxetine than for tricyclic drugs,⁵ although both types of drug led to similar improvement in suicidal ideation with treatment.

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Commercial interests should not influence prescribing

EDITOR,—N Freemantle and colleagues analysed the cost effectiveness of a preference for selective serotonin reuptake inhibitors over older tricyclic antidepressants as a strategy for preventing suicide.¹ Apart from the debate about which antidepressant to prescribe there seems to be little discussion about other prescribing strategies that might reduce the risk of suicide. Dextropropoxyphene (alone and in combinations) has a higher fatal toxicity index than imipramine,² and co-proxamol is implicated in at least half as many accidental and suicidal deaths as are tricyclic antidepressants.³ Despite this and despite evidence that co-proxamol is probably no more effective than simple analgesics and is potentially dangerous in elderly people,⁴ co-proxamol remains the most commonly prescribed analgesic in primary care.