Authors' reply

EDITOR,—Our paper aimed at estimating the cost effectiveness of a strategy of changing antidepressant prescribing for reducing suicides due to antidepressant poisoning, which account for between about 298 and 432 deaths each year. Because of problems of (commercial) confidentiality in reporting prescribing analysis and cost (PACT) data we considered classes of drugs rather than individual products. The higher toxicity of maprotiline in overdose is reflected in the observational suicide data we reported. Philip Cowen and Chris Thompson and Ann Roberts interpret the evidence as suggesting that prescribing lofepramine may be the most cost effective option for reducing suicide, but they misunderstand our use of the World Health Organisation's defined daily dose tables, which are not guidelines for prescribing but a representation of prescribing in practice.¹ At the higher dose lofepramine remains more cost effective for preventing suicide than fluoxetine (the cheapest selective serotonin reuptake inhibitor at current market prices) (see table). The analysis indicates to the industry the price at which products may become cost effective for this purpose.

Cost (£) per life year saved by preventing fatal poisoning with older tricyclic antidepressants through prescribing fluoxetine or high dose lofepramine at current market prices

Relapse rate (%)	Fluoxetine (20 mg/day)*		Lofepramine (210 mg/day)†	
	432 Suicides prevented	298 Suicides prevented	432 Suicides prevented	298 Suicides prevented
	Rate of effect 80%			
0	19 080	27 659	14 225	20 015
10	21 039	30 500	15 686	22 071
	Rate of effect 60%			
0	25 440	36 879	18 967	26 687
10	28 052	40 666	20 915	29 427

Cost per 28 days: *£20, †£14.96.

Some correspondents attempt to broaden the potential benefits of prescribing selective serotonin reuptake inhibitors to attempted suicide and road traffic accidents. As the Canadian guidelines on economic evaluation of pharmaceuticals state, however, analyses of cost effectiveness compare drugs or programmes having a common health outcome,² in this case suicide. Although a full cost-benefit analysis comparing all the costs and benefits of treatments for depression would be desirable, insufficient data are available.

In criticising our previous meta-analysis and quoting their favoured review³ correspondents fail to mention that the latter analysis was based on selective use of the available clinical trials, was published in a journal edited by the lead author, and was simultaneously promoted by Pfizer.⁴ The main outcome measure reported by Montgomery *et al.*—discontinuation of treatment because of side effects—is open to biased assessment and is reported in only a (non-random) sample of studies. There is no evidence that antidepressants differ greatly in tolerability or that tolerability is a major cause of undertreatment of depression in people who subsequently kill themselves.⁵

None of the correspondents present reliable evidence (as opposed to opinion) that refutes our general conclusions. We are not alone in questioning the benefits of a widespread shift in prescribing to selective serotonin reuptake inhibitors,⁶ which cannot be justified by currently available evidence, and we welcome the call from D Tracey and Robin Gonzaga and Prakash Naik for a more reasoned debate of the issues.

Papers such as ours that question the promotional claims of the pharmaceutical industry or other vested interests commonly provoke numerous critical responses, which are often

aimed at discrediting the authors and baffling readers rather than advancing scientific debate. This presents a serious problem for journal editors, policymakers, and clinicians. As the deputy editor of the *Journal of the American Medical Association* noted, "When these citations are laid before a busy legislator . . . who lacks the scientific training required to assess their content, will he or she know they are merely letters and be able to gauge the weight of these contributions as opposed to their number?"⁷

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1 World Health Organisation Collaborating Centre for Drug Statistics Methodology. *Anatomical therapeutic chemical (ATC) classification index*. Geneva: WHO, 1993.

2 Canadian Coordinating Office for Health Technology Assessment. *Guidelines for economic evaluation of pharmaceuticals*. Canada: Ottawa: CCOHTA, 1994.

3 Montgomery SA, Henry J, McDonald G, Dinan T, Lader M, Hindmarch I, *et al.* Selective serotonin reuptake inhibitors: meta-analysis of discontinuation rates. *Int Clin Psychopharmacol* 1994;9:47-53.

4 *Setting the record straight: the evidence for using SSRIs instead of TCAs in the first line treatment of depression—press information*. Surrey: Medical Action Communications and Invicta Pharmaceuticals, Pfizer, 1994.

5 Isacson G, Holmgren P, Wasserman D, Bergman U. Use of antidepressant medication among people committing suicide in Sweden. *BMJ* 1994;308:506-9.

6 Selective serotonin reuptake inhibitors for depression? *Drug Ther Bull* 1993;31:57-8.

7 Rennie D. Smoke and letters. *JAMA* 1993;270:1742-3.

Subfertility in men

Measurement error and confounding not accounted for

EDITOR,—Richard Lilford and colleagues conclude that subfertility in men is familial and that their observations are consistent with a genetic cause.¹ Measurement error and confounding may provide alternative explanations.

In case-control studies it is essential that the data collected from cases and controls should be of comparable accuracy—a requirement not met by this study, in which infertility in the brothers of cases and controls was assessed on hearsay evidence. The reasons for childlessness are more likely to be explored when two brothers are childless than when one brother is fertile and the other childless. Subfertile men may actively seek the explanation of their brother's childlessness in an attempt to explain their own subfertility. Cases and controls may interpret unexplained childlessness from their own experience as involuntary or voluntary. Additional bias may be introduced if the collection of information was not blinded. The use of reported childlessness also assumes that all such childlessness is due to male subfertility, the partner's contribution being ignored. Misclassification could easily explain these results.

We agree that the difference in total childlessness between the two groups is unlikely to have been inaccurately reported. The decision to have children, however, is confounded by demographic, cultural, and social factors,² many of which are familial and not controlled for in this study. This would explain the significant difference in total childlessness between the two groups. It would

also argue against the view that voluntary childlessness should be the same in both groups, a point used to reassure us that bias was not present in this study.

The investigators are left with evidence from three family trees in which male subfertility was traced. Familial clustering in male infertility is an interesting finding, but to base a hypothesis of genetic transmission on such evidence seems perilous in the extreme. The relatively high prevalence of subfertility in the general population seems a more plausible explanation.³

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1 Lilford R, Jones AM, Bishop DT, Thornton J, Mueller R. Case-control study of whether subfertility in men is familial. *BMJ* 1994;309:570-3.

2 The management of subfertility. *Effective Health Care* 1992; No 3.

Congenital abnormality may play a part

EDITOR,—Richard Lilford and colleagues report a significant increase in involuntary childlessness among male relatives of subfertile men but have not considered one possible explanation for their findings.¹ Two per cent of men attending infertility clinics have congenital bilateral absence of the vas deferens.² About 50-70% of men with this abnormality have mutations in the cystic fibrosis transmembrane receptor gene. As most of these men are heterozygotes they are likely to be asymptomatic. We therefore suggest that it would be valuable to screen the study population for the mutations in the cystic fibrosis transmembrane receptor gene known to be associated with congenital bilateral absence of the vas deferens. Familial transmission of mutations causing the abnormality may explain the familial subfertility found in this study, which seemed to affect male rather than female relatives.

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1 Lilford R, Jones AM, Bishop DT, Thornton J, Mueller R. Case-control study of whether subfertility in men is familial. *BMJ* 1994;309:570-3. (3 September.)

2 Congenital bilateral absence of the vas deferens and CF [editorial]. *Lancet* 1992;336:512.

Author's reply

EDITOR,—Gregson and colleagues suggest potential biases to which we had already drawn attention in our article. We explained that it was not possible to corroborate the histories in most cases because of the sensitivity of this subject. We therefore devoted considerable attention to the possibility that information about infertility may be transferred more readily in the families of probands. The reported incidence of subfertility was not, however, increased among sisters of probands compared with controls. Such biased reporting would therefore have had to be specific to brothers rather than siblings.

Furthermore, we dealt thoroughly with the point that some childlessness may be due to subfertility in female partners. This bias, however, would be one of the many working against our hypothesis, since any subfertility due to female factors would dilute the pool of subfertile men who might have a subfertile brother. It is important, in clinical epidemiology, to consider not only the