Most suicides are probably not preceded by depressive illness.[3] When depression is present, antidepressants may not be prescribed[3]; this may be an appropriate clinical decision in many instances. The likelihood of non-compliance with prescribed drug treatment is high.[5] It is unfortunate that Isacsson and colleagues did not examine medical records for the people who died, specifically for whether psychotropic drugs had been prescribed to estimate the prevalences of prescribing of antidepressants and non-compliance in this population.

The reported data do not support Isacsson and colleagues' conclusion that compounds with lower toxicity were found more commonly than conventional tricyclic drugs relative to their overall use. The standardised mortality ratios clearly indicate that lofepramine differs appreciably from the other tricyclic drugs in a favourable manner. Regrettably, no selective serotonin reuptake inhibitors are included in this dataset. It is interesting that clomipramine, as Cassidy and Henry found,[2] may differ from the other tricyclic drugs with regard to toxicity. Isacsson and colleagues have provided additional support for the proposition that the prescription of non-toxic, newer antidepressant drugs such as lofepramine is warranted.

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Authors' reply

EDITOR,—We studied 3400 suicides during two years in Sweden; probably half of these suicides were committed by people who were depressed. Measurable concentrations of antidepressants were found in only 542 cases, while possibly lethal concentrations were found in 190. This may imply that underprescribing and therapeutic failure are greater problems than toxicity with antidepressant drugs. As moclobemide and mianserin were found twice as commonly as we expected from their prescribing we concluded that our result did not indicate any advantage of less toxic antidepressants. The risks associated with lofepramine (and mianserin) may further be falsely low because of a lower sensitivity for these drugs in the analytical method used.

As we pointed out, our survey was not experimental and there were many possible confounders, one being selective prescribing. In a questionnaire survey we found mianserin, moclobemide, and lofepramine to be more commonly chosen for depressed patients with suicidal tendencies (paper in preparation). This would modify the increased risk associated with mianserin and moclobemide and enhance the reduced risk associated with lofepramine. The most cited paper regarding toxicity in overdose concludes: "If the newer drugs have as good a record of clinical effectiveness, combined with their lower potential to cause fatal poisoning when taken in overdose, serious consideration should be given to preferentially prescribing the newer drugs, especially to patients who are considered at particular risk of suicide by ingestion of an overdose of their medication."[1]

The important prerequisite—whether these newer drugs really are as effective as the older tricyclic agents—has not been given much attention. Controlled clinical trials show that several new, less toxic antidepressants, including selective serotonin reuptake inhibitors paroxetine and citalopram, are less effective in the treatment of depression.[2] Data from seven large published comparative clinical trials, of which five were included in a recent review on moclobemide, show that the drop out rate due to insufficient effect, worsening symptoms, suicidality, or suicide is two to three times higher in patients treated with moclobemide than in those treated with tricyclic or tetracyclic drugs.[3,4]

We believe that the main problems in using antidepressants to prevent suicide is that too many cases of depression are not diagnosed, too many people diagnosed as having depression are not treated with antidepressants, and too many patients treated with antidepressants fail to respond because of inadequate dosing, non-compliance, or a relative ineffectiveness of the drug. Focusing on the small proportion of suicides that are due to overdose of tricyclic antidepressants will discourage doctors from using these drugs effectively and encourage non-systematic use of newer drugs.

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Dietary treatment of hyperlipidaemia

Diets were poorly evaluated

EDITOR,—It is ironic that Douglas G Altman's editorial castigating poor medical research[1] should appear one week after the paper by Angela A Rivellese and colleagues, which concluded that two test diets "are suitable for treatment of hypercholesterolaemia."[2] There are many problems with this study.

The study is indeed controlled in the sense that its design permitted a valid comparison of the low total fat and high unsaturated fat diets. The statistical power was not, however, sufficient to exclude a meaningful difference between the diets, as the authors maintain. The confidence intervals indicate that the effect of the two diets on total cholesterol concentration, for example, could easily differ by as much as 7%. To put this in context, the efficacy claimed for the diets when compared with the "control" phase was only 8-9%.

The authors' main message, however, had nothing to do with the comparison of the diets but focused on the supposed efficacy of the diets. Efficacy was assessed by a before and after comparison back to the three week "control" period, a method that is open to many sources of error and bias. Furthermore, the diet during the control period was evidently not the normal diet for the subjects because it was identical for each subject. This control diet succeeded in increasing total cholesterol concentration significantly to a spuriously high baseline value, from which the intervention diets were launched. Use of the true baseline values show that the low total fat diet reduced total cholesterol concentration by only 3% and the high unsaturated fat diet by only 1%. Even these small changes in cholesterol concentration were achieved only by ignoring the substantial number of subjects who would not continue the diets even for six months—18% for the low total fat and 43% for the high unsaturated fat diet. No intention to treat or final state analysis was presented.

How can the authors conclude that these diets are suitable for treatment of hypercholesterolaemia when the study design was flawed; the effect on lipids was so small; the diets were poorly tolerated; and the final total cholesterol concentration remained about 30% above the 5·0-5·2 mmol/l target suggested in most guidelines? This paper highlights the double standards that prevail for the evaluation of non-pharmacological treatments compared with the evaluation of new drugs. Any pharmaceutical company approaching a regulatory authority with a study like this to support the efficacy and tolerability of a drug would get short shrift. Hard questions ought to be put to the referees who assessed this paper.

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Authors' reply

EDITOR,—The possibility of lowering plasma cholesterol concentrations by reducing saturated fat intake represented the background rather than the objective of our study. Nowadays there is no reason to study the efficacy of low saturated fat diets: this was shown in the 1960s and confirmed by 27 controlled studies.[1,2]

If it is scandalous to misinterpret one's own results,[3] how should the misinterpretation of other people's results be considered? A 7% (or greater) difference in plasma cholesterol concentrations between the two test diets that we evaluated has only a 5% probability of occurring; yet Lawrence E Ramsay and colleagues distort the statistical meaning of the confidence intervals, stating that such a difference could easily be found.

If this same criterion was applied to the evaluation of studies testing the efficacy of drugs even the Lipid Research Clinics study (which has had a huge impact on medical behaviour) would get extremely short shrift from a regulatory authority. In that study the group treated with cholestramine experienced a 19% reduction in the risk of myocardial infarction compared with the placebo group, although the confidence interval ranged from 3% to 32%.[4] Who would consider a hypocholesterolaemic drug to be effective if its ability to