Suicide and the use of antidepressants

Drug treatment of depression is inadequate

EDITOR,—Göran Isacsson and colleagues suggest that therapeutic failure of antidepressant drugs may be a greater problem in people who commit suicide than toxicity in overdose as their results indicated no advantage of the newer, less toxic drugs; furthermore, their results confirmed that only a small minority of people who commit suicide have received antidepressant treatment before death despite the high prevalence of depression in the population.[1] The notable problems in their otherwise impressive database were, however, that they had neither diagnostic information nor knowledge of the dosage used in the cases studied. As our work may contribute to these questions,[2] we wish to confirm and extend their findings.

In the national suicide prevention project in Finland all suicides (n = 1397) in Finland committed between 1 April 1987 and 31 March 1988 were comprehensively examined by the psychological necropsy method. Mental disorders were evaluated retrospectively, according to the criteria in the *Diagnostic and Statistical Manual of Mental, Disorders*, third edition, revised, in a diagnostic study of a random sample of 229 suicides.[3] In this study 71 of the 229 people who had committed suicide were estimated to have had current unipolar major depression.

Further examination of these 71 people showed that only 22 out of 66 (33%) had received antidepressant treatment (the information concerning possible antidepressant treatment was insufficient in four cases and conflicting in one)[2]—a finding similar to the proportion (30%) reported by Barraclough *et al* in West Sussex.[4] Most notably, only two people had received antidepressants in adequate doses (doxepin 250 mg/day and mianserin 60 mg/day). None of the others had received more than an equivalent of 100 mg of a tricyclic antidepressant daily. Thus only 3% (2/66) of people with current major depression who committed suicide were receiving adequate antidepressant treatment.[2]

In our study population, which effectively represented all suicides among people with major depression in Finland, only 8% (6/71) committed suicide by taking an overdose of antidepressant (three cases of intoxication with other psychopharmacological agents were also found).[2] Most of the people with major depression who committed suicide, especially men, used violent methods, even if they were receiving drug treatment. A finding with implications for future studies using prescription databases was that in four of the nine cases of suicide due to intoxication with psychopharmacological agents the drug taken in overdose was not currently being used for treatment.[2] Thus depressed people may save drugs from earlier treatment periods and use them in a lethal overdose. A fatal toxicity index reflects the risk of fatal overdose per prescriptions in the population, but this may be different from the risk per current period of treatment with the particular drug.

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1 Isacsson G, Holmgren P, Wasserman D, Bergman U. Use of antidepressants among people committing suicide in Sweden. *BMJ* 1994;308:506-9. (19 February.)
2 Isometsä ET, Henriksson MM, Aro HM, Heikkinen ME, Kuoppasalmi KI, Lönnqvist JK. Suicide in major depression. *Am J Psychiatry* 1994;151:530-6.
3 Henriksson MM, Aro HM, Martunnen MJ, Heikkinen ME, Isometsä ET, Kuoppasalmi KI, *et al.* Mental disorders and comorbidity in suicide. *Am J Psychiatry* 1993;150:935-40.
4 Barraclough BM, Bunch J, Nelson B, Sainsbury P. A hundred cases of suicide: clinical aspects. *Br J Psychiatry* 1974;125: 355-73.

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Nearly a third of deaths related to poisoning

EDITOR,—In their study examining the detection of antidepressants at postmortem examination Göran Isacsson and colleagues concluded that, because few suicides are associated with toxic concentrations of antidepressants and the newer, less toxic antidepressants seem to be overrepresented in relation to their estimated use, therapeutic failure may be more important than toxicity.[1] Although the use of antidepressants was standardised for age, sex, and geographical area when rates of detection in cases of suicide were compared, two further potential confounding factors were not addressed. Firstly, in cases in which clinicians were concerned about the possibility of suicide they probably prescribed less toxic drugs. Secondly, patients who had longstanding depression resistant to treatment had probably been prescribed newly developed antidepressants, and a higher rate of suicide would be expected in this group. Both of these factors would result in an overrepresentation of the less toxic drugs mianserin and moclobemide in cases of suicide.

The data presented show that 190 of the 585 patients who were taking antidepressants at the time of death had a toxic concentration of these drugs. This suggests that up to 30% of deaths in these patients had been caused by overdose of antidepressant. Contrary to the authors' conclusion, toxicity may be of the utmost importance in patients who are taking antidepressants.

The study was useful in emphasising the apparent underuse of antidepressant drugs by patients who commit suicide. But it is not possible to conclude that therapeutic failure is more important than toxicity; indeed, toxicity may be an important cause of death in patients prescribed antidepressants.

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Patients at greatest risk given newer drugs

EDITOR,—Göran Isacsson and colleagues report that most depressed patients who commit suicide are not taking antidepressants immediately before their death and that therapeutic failure may be a greater problem with antidepressants than toxicity.[1] I agree that the results may be explained by the authors' hypothesis that mianserin and moclobemide are less effective than tricyclic antidepressants. I wish, however, to propose an alternative explanation—namely, that these newer drugs, because of their greater safety in overdose, may have been preferentially prescribed to patients judged to be at higher risk of suicide. A history of parasuicide is a known predictor of the risk of suicide in the future; when faced with a patient with such a history, practitioners may opt for a less toxic alternative to the older antidepressants. (Personal experience and discussion with colleagues suggest that this is often the case.)

The conclusion that newer, less toxic antidepressants seem more likely to result in therapeutic failure is open to misinterpretation. The new antidepressants with low toxicity that are most widely prescribed in Britain are the selective serotonin reuptake inhibitors, which were not examined in detail by this study. It would have been more accurate to restrict this statement to mianserin and moclobemide.

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Depression may not precede suicide

EDITOR,—Göran Isacsson and colleagues attempted to address an important psychopharmacological issue—namely, whether different classes of antidepressant drugs have differential effects on suicidality.[1] Tricyclic drugs are toxic in overdose,[2] and taking them is an effective method of suicide. Most suicides, however, are not due to overdose of antidepressants.[3] It is more relevant to consider the relative potency of the antidepressant effect and the effect on suicidality when comparing tricyclic with non-tricyclic drugs. There are minimal data on which to base firm conclusions.

We wish to challenge some of the assumptions that underpin this paper. The authors' stated objective was "to analyse the outcome of depression as reflected by detection of antidepressants" in a sample of unnatural deaths. An assumption that suicide is almost invariably preceded by depression is incorrect. Recent studies estimate that between 34·6%[3] and 66%[4] of suicide victims may have suffered from depression.

The proportion of people who died with evidence of antidepressant drugs in their blood is low, being 15·9% (542/3400) among the suicide cohort and 7·7% (542/7000) among the total deaths examined. Similarly, the proportion who died with toxic concentrations of antidepressant drugs is low, being 5·6% (190/3400) and 2·7% (190/7000) respectively. The authors concluded that these findings implied failure to detect and treat depressive illness effectively. This may be correct, but alternative explanations must be considered.

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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1 Isacsson G, Holmgren P, Wasserman D, Bergman U. Use of antidepressants among people committing suicide in Sweden. *BMJ* 1994;308:506-9. (19 February.)
2 Cassidy SL, Henry JA. Fatal toxicity of antidepressant drugs in overdose. *BMJ* 1987;295:1021-4.
3 Milne S, Matthews K, Ashcroft GW. Suicide in Scotland 1988-89: psychiatric and physical morbidity according to primary care notes. *Br J Psychiatry* (in press).
4 Henriksson MM, Aro HM, Marttunen MJ, Heikkinen ME, Isometsa ET, Kuoppasalmi KI, *et al.* Mental disorders and comorbidity in suicide. *Am J Psychiatry* 1983;150:935-40.
5 Myers ED, Branthwaite A. Out-patient compliance with antidepresant medication. *Br J Psychiatr* 11992;160:83-6.

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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1 Cassidy S, Henry J. Fatal toxicity of antidepressant drugs in overdose. *BMJ* 1987;295:1021-4.
2 Danish University Antidepressant Group (DUAG). Moclobemide: a reversible MAO-A inhibitor showing weaker antidepressant effect than clomipramine in a controlled multicenter study. *J Affect Disord* 1993;28:105-16.
3 Freeman H. Moclobemide. *Lancet* 1993;342:1528-32.
4 Gram LF, Isacsson G, Bergman U. Moclobemide. *Lancet* 1994;343:679-80.

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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1 Altman DG. The scandal of poor medical research. *BMJ* 1994;308:283-4. (29 January.)
2 Rivellese AA, Auletta P, Marotta G, Saldalamacchia G, Giacco A, Mastrilli V, *et al.* Long term metabolic effects of two dietary methods of treating hyperlipidaemia. *BMJ* 1994;308:227-31. (22 January.)

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