populations, with variable doses and durations, which creates further difficulty in interpreting such data. We therefore conclude that it is not possible to state with certainty which of the seven most commonly prescribed non-steroidal anti-inflammatory drugs is the safest; six of these seven have similar profiles of adverse events.

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1 Bradlow A, David J. Recent advances in rheumatology. *BMJ* 1995;309:637-40. (11 March.)
2 Committee on Safety of Medicines, Medicines Control Agency. Relative safety of oral non-aspirin NSAIDs. *Current Problems in Pharmacovigilance* 1994;20:9-11.
3 Figueras A, Capella D, Castel JM, Laporte JR. Spontaneous reporting of adverse drug reactions to non-steroidal anti-inflammatory drugs. *Eur J Clin Pharmacol* 1994;47:297-303.
4 Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk of peptic ulcer disease in elderly persons. *Ann Intern Med* 1991;114:257-63.

Antidepressants and suicide

Study analyses were flawed

EDITOR,—Two recent articles look at use of antidepressants and death from suicide. John A Henry and colleagues have continued previous work and assessed the relation between death and defined daily dose.¹ Unfortunately, the defined daily dose for dothiepin used in the paper (75 mg) should be 150 mg (references quoted by Henry and colleagues). The correct figure is then 3.08 deaths per million defined daily doses of dothiepin instead of 1.54—the second highest figure, after that for amoxapine. This agrees with a clinical study that showed that dothiepin has greater toxicity in overdose than other tricyclic antidepressants.² We are also concerned about the statistical methods used by Henry and colleagues. It is unclear how valid confidence limits are in this context without a clear definition of x and how the standard error (no deviation) was calculated. It is inappropriate to use one tailed tests of significance without a prior hypothesis, and it is incorrect to use Fisher's exact test to compare rates.

In the study by Susan S Jick and colleagues we question the inclusion of flupenthixol, which is more likely to be used for schizophrenia than depression and is usually used as a depot preparation.³ Also, the overall suicide rate of 8.3 per 10 000 person years of antidepressant use seems remarkably low and is much lower than rates in affective disorder cited in the literature.⁴ The data from Henry and colleagues' paper give a death rate for poisoning with dothiepin alone of 11.25 per 10 000 person years of use.¹ These discrepancies raise three possibilities. One is that prescribers were using antidepressants mainly for conditions other than affective disorder. Another is that suicide was considerably underestimated in the cohort. In Henry and colleagues' study only 56% of the deaths due to poisoning were suicides, the remainder being undetermined. To ignore these deaths when comparing outcome may obscure differences in toxicity between antidepressants in overdose. Thirdly, there was systematic underdosing of the antidepressants in the study compared with the defined daily dose. Obviously, combinations of all three factors may have occurred.

Finally, Jick and colleagues comment that their data are consistent with the proposition that those who are determined to commit suicide will find a way that produces the intended outcome. This

comment would be supported only if they could show that patients on their database who survived self poisoning went on to commit suicide by other means. This is not supported by the literature, which indicates that most patients who survive after taking an overdose do not subsequently kill themselves by other means.⁵

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1 Henry JA, Alexander CA, Sener EK. Relative mortality from overdose of antidepressants. *BMJ* 1995;310:221-4. (28 January.)
2 Buckley NA, Dawson AH, Whyte IM, Henry DA. Greater toxicity in overdose of dothiepin than other tricyclic antidepressants. *Lancet* 1994;343:159-62.
3 Jick SS, Dean AD, Jick J. Antidepressants and suicide. *BMJ* 1995;310:215-8. (28 January.)
4 Tanney EL. Mental disorders, psychiatric patients, and suicide. In: Maris RW, Berman AL, Maltzberger JT, Yufit RJ, eds. *Assessment and prediction of suicide*. New York: Guilford Press: 1992:277-320.
5 Nordentoft M, Breum L, Munck LK, Nordestgaard AG, Hunding A, Bjaeldager PAL. High mortality by natural and unnatural causes: a 10 year follow up study of patients admitted to a poisoning treatment centre after suicide attempts. *BMJ* 1993;306:1637-41.

Study is based on unproved assumptions

EDITOR,—John A Henry and colleagues draw several familiar conclusions from their study of suicide and antidepressants.¹ They argue that their data "provide a useful guide to the relative toxicities of drugs and an indication of the needs for prescribing policy" and suggest that a considerable number of suicides could be prevented by a switch to routine prescribing of selective serotonin reuptake inhibitors. This opinion is not always expressed in such restrained terms—as the accompanying editorial reminds us²—and yet it is based on two unproved assumptions. The first is that relative mortality due to overdose is the same as relative toxicity in overdose. The second is that suicidal patients prescribed a non-toxic drug will not seek an alternative means of killing themselves.

Since the data on relative mortality due to an overdose of antidepressants do not come from randomised trials they could reflect differences between patients prescribed different antidepressants rather than differences between the drugs themselves. There is evidence to support this interpretation. For example, when Farmer and Pinder derived a similar "toxicity" index using data from Intercontinental Medical Statistics they found that for each antidepressant the index was lower in those aged over 65 than in younger people³; this cannot be reconciled with the suggestion that the index reflects cardiotoxicity in overdose. If the index measures drug toxicity then it should be stable over time; in fact, the index for amitriptyline calculated for the years 1975-84 is 46.5 (95% confidence interval 43.9 to 49.1)⁴ and for the years 1987-92 is 38.9 (35.6 to 42.4).⁵

If antidepressants do differ in toxicity in overdose it does not follow that routine prescribing of drugs with lower toxicity will reduce the suicide rate. Such a conclusion would be justified only if there was no substitution of method—in other words, if the prescription of a more toxic drug offered an opportunity for suicide that the depressed person would not find elsewhere. The study by Susan S Jick and colleagues substantially undermines this "loaded gun" argument against the tricyclic drugs since its main finding is that prescription of an older tricyclic antidepressant (rather than a new drug) does not constitute a risk factor for suicide.⁶

Contrary to the conclusions of this paper, there

is uncertainty about the true difference in toxicity of different antidepressants in overdose and about the effect of substitution of method in a suicide prevention strategy based on prescribing policy. The small number of lives that might potentially be saved by prescribing the selective serotonin reuptake inhibitors must be set against the costs. Our cost effectiveness study showed how expensive such a prescribing policy might be when compared with other public health policies,⁶ even when the calculations were based on assumptions compatible with the data presented by Henry and colleagues. These latest studies do nothing to challenge our conclusion that a widespread move to prescribing specific serotonin reuptake inhibitors as first line treatment for depression cannot be justified on the evidence available.

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1 Henry J, Alexander C, Sener E. Relative mortality from overdose of antidepressants. *BMJ* 1995;310:221-4. (28 January.)
2 Edwards JG. Suicide and antidepressants. *BMJ* 1995;310:205-6. (28 January.)
3 Farmer R, Pinder R. Why do fatal overdose rates vary between antidepressants? *Acta Psychiatr Scand* 1989;80(suppl 354): 25-35.
4 Cassidy S, Henry J. Fatal toxicity of antidepressant drugs in overdose. *BMJ* 1987;295:1021-4.
5 Jick SS, Dean A, Jick H. Antidepressants and suicide. *BMJ* 1995;310:215-8. (28 January.)
6 Freemantle N, House A, Song F, Mason J, Sheldon T. Selective serotonin reuptake inhibitor prescribing as a strategy for the prevention of suicide. *BMJ* 1994;309:249-53.

Study did not consider treatment efficacy

EDITOR,—The papers on suicide and antidepressants in the issue of 28 January develop our understanding of this problem further. John A Henry and colleagues point out the differences in the rate of death by overdose for different antidepressants¹ but fail to relate this to efficacy and the fact that only 4-5% of all suicides are due to an overdose of antidepressant.² Susan S Jick and colleagues show that many people taking antidepressants commit suicide but do not give data on the number of suicides that occur in untreated depressed patients.³ Interestingly, they found a distinct difference in crude rates of suicide between people taking tricyclic antidepressants (7.4 (range 4.7-8.7) suicides/10 000 person years) and people taking non-tricyclic antidepressants (flupenthixol, mianserin, fluoxetine, or trazodone; 14.9 (12.0-19.0) suicides/10 000 person years). The further analyses of fluoxetine, the antidepressant with the highest crude rate of suicide (19.0/10 000 person years), suggested that this rate could partly be explained by selection bias, in particular related to "history of suicidal behaviour." There seemed, however, to be "residual factors which reflected a higher risk of suicide for subjects taking fluoxetine."

Evidence suggests that the selective serotonin reuptake inhibitors (such as fluoxetine) are less effective than the tricyclic antidepressants, particularly in the more severe melancholic type of depression.⁴ If patients with this type of depression constitute an appreciable proportion of those at risk of committing suicide then the earlier recommendations, based on data on the toxicity of drugs in overdose, that the tricyclic antidepressants should be abandoned may have contributed to an increase in the overall rate of suicide. As was pointed out in a similar debate a year ago, the

problem of efficacy has to be incorporated into the discussion on antidepressants and suicide.² That debate arose from a Swedish study analogous to that of Jick and colleagues, in which a large proportion of the patients committing suicide had not taken antidepressants.² Interestingly, in that study mianserin and moclobemide were associated with a high rate of suicide relative to their overall consumption. Several clinical reports suggest that moclobemide is less effective than tricyclic antidepressants.

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higher overall suicide rate—for example, the adjusted relative risk for fluoxetine was 2.1 times that for dothiepin² and the standardised mortality ratio for suicide associated with mianserin was twice that associated with amitriptyline.³ Authors of both studies addressed the issue of biases that might have arisen because of non-random allocation of patients to antidepressant type. We think, however, that the conclusion that one might reduce the suicide rate by preferentially prescribing the newer antidepressant drugs is unwarranted.

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- 2 Jick SS, Dean AD, Jick H. Antidepressants and suicide. *BMJ* 1995;310:215-8. (28 January.)
- 3 Isacson G, Holmgren P, Wasserman D, Bergman U. Use of antidepressants among people committing suicide in Sweden. *BMJ* 1994;308:506-9.
- 4 Song F, Freemantle N, Sheldon T, House A, Watson P, Long A, et al. Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *BMJ* 1993;306:683-7.
- 5 Roose S, Glassman A, Attia E, Woodring S. Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. *Am J Psychiatry* 1994;151:1735-9.

The two study groups may not be comparable

EDITOR,—Susan S Jick and colleagues conclude their detailed study of suicide and prescribing of antidepressants by stating that their data are consistent with the hypothesis that those who are determined to commit suicide will do so even if one particular means (drug overdose) is made less available.¹ Such a view is also supported by J Guy Edwards in his accompanying editorial.² The data presented do not support these assertions.

In Jick and colleagues' study overall crude suicide rates were twice as high in the group who took other antidepressants (14.9/10 000 person years) as in those taking tricyclic antidepressants (7.4/10 000). This suggests that there may be differences between the two groups that were not adjusted for in the analysis (as adjustment for age, sex, and calendar year made little difference to the relative risks quoted). Such differences may include diagnosis and severity of depression, which may in turn affect risk of suicide; the effects of these factors were examined in only a subsample of patients. Unadjusted rates of suicide due to an overdose were no higher in those prescribed tricyclic antidepressants (2.9/10 000 person years) than in those prescribed the four other antidepressants included in the analysis (3.1/10 000). Eight of the 104 suicides in those taking tricyclic antidepressants were a result of overdose of antidepressant while none of the 39 suicides in those taking non-tricyclic antidepressants were; the difference does not reach conventional levels of significance (two tailed Fisher's exact $P=0.1$). Patients taking non-tricyclic antidepressants used other drugs more often for overdose. The incidence of failed suicide attempts is not reported. The authors' inference is that patients taking antidepressants other than tricyclic antidepressants knew that their drugs were less toxic in overdose. These observational data do not support or refute the "method availability hypothesis"; only by more complete adjustment for confounding can this issue in this group of patients be examined.

Edwards also suggests that people who are determined to kill themselves will find a means of doing so. He cites data on time trends in rates of suicide by particular methods; such trends may, however, be subject to different interpretations. Rates of suicide by particular methods differ by age

and sex.³ Increases in the use of violent methods and decreases in suicide due to overdose may be associated with the increase in suicide among young males (who more often use violent methods or carbon monoxide poisoning) and the decrease in suicide among females (who more often use overdose).

Evidence suggests that limitations on the ready availability of methods deter some people from committing suicide.⁴ Changes in domestic gas supply as well as reduced use of barbiturates are thought to have prevented over 6700 suicides in the 1960s in Britain.⁵ Restricting the availability of methods exploits the ambivalence felt by many would be suicides and buys time during which the suicidal impulse may pass. There is clearly more to preventing suicide than limiting access to means. Social policy measures and recognition and treatment of depression may be equally important. Possible interventions to reduce suicide by decreasing the availability of particular methods have been described; some of these measures include modifications to prescribing practices, and the evidence presented by Jicks and colleagues and Edwards does not refute these suggestions.⁶

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- 1 Jick SS, Dean AD, Jick H. Antidepressants and suicide. *BMJ* 1995;310:215-8. (28 January.)
- 2 Edwards JG. Suicide and antidepressants. *BMJ* 1995;310:205-6. (28 January.)
- 3 Charlton J, Kelly S, Dunnell K, Evans B, Jenkins R, Wallis R. Trends in suicide deaths in England and Wales. *Population Trends* 1992;69:0-6.
- 4 Clarke RV, Lester D. *Suicide: closing the exits*. New York: Springer Verlag, 1989.
- 5 Office of Health Economics. *Suicide and deliberate self-harm*. London: OHE, 1981.
- 6 Gunnell D, Frankel S. Prevention of suicide: aspirations and evidence. *BMJ* 1994;308:1227-33.

Antidepressants prescribed for conditions other than depression

EDITOR,—Susan S Jick and colleagues' study on the use of antidepressants, based on data from the VAMP database, and rates of suicide may result in more confusion than elucidation.¹ It is not clear whether the initial hypothesis was that observed suicide rates were evidence of failure to control depression, with consequent suicide, or that the agents were themselves a causative factor. The distinction is important since one case deals with inefficacy and the other with an adverse reaction. No data are provided on the suicide rate in the British population, in all the patients on the database, or in a comparative group of patients. Risk factors are compared between patients who have successfully committed suicide and a group who have unsuccessfully attempted suicide, even though they may have tried on many occasions.

The analyses of relative risk leave unaddressed a major confounding factor—namely, the numerous non-depressive conditions for which these agents are used. The IMS MediPlus database shows that about a fifth of prescriptions for selective serotonin reuptake inhibitors are for diagnoses other than depression; for amitriptyline and dothiepin the proportion is over a quarter. In the special case of imipramine, roughly 35% of its use is for disorders of micturition (44% for Tofranil). These are high proportions, and adjustment should be made for them in any assessment that differentiates products in terms of relative risk unless the objective was specifically to evaluate suicide as an adverse reaction.

Data available to Jick and colleagues extended to only February 1993 and so are now two years out of date. This is a serious problem, since the advent of selective serotonin reuptake inhibitors has

- 1 Henry JA, Alexander CA, Sener EK. Relative mortality from overdose of antidepressants. *BMJ* 1995;310:221-4. (28 January.)
- 2 Isacson G, Holmgren P, Wasserman D, Bergman U. Use of antidepressants among people committing suicide in Sweden. *BMJ* 1994;308:506-9.
- 3 Jick SS, Dean AD, Jick H. Antidepressants and suicide. *BMJ* 1995;310:214-8. (28 January.)
- 4 Roose SP, Glassman AH, Attia E, Woodring S. Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. *Am J Psychiatry* 1994;151:1735-9.
- 5 Isacson G, Holmgren P, Wasserman D, Bergman U. Suicide and the use of antidepressants. *BMJ* 1994;308:916.

Study's conclusion is unwarranted

EDITOR,—We believe that one of the key messages in the paper by John A Henry and colleagues is misleading: it states that "deaths from overdose can be prevented by switching prescribing from older, tricyclic drugs; such a move may contribute to government targets for reducing suicide."¹ The same point is made in the last paragraph of the paper. The flaw is to equate the prevention of fatal poisoning with that of suicide in general. In the same issue Susan S Jick and colleagues found that of 143 suicides in Britain, only eight (6%) were due to antidepressant overdose.² Similarly, in Sweden 190 (6%) of 3400 people who committed suicide had toxic blood antidepressant concentrations.³ The figure for England and Wales in 1990 was 7%. Thus the overwhelming majority of suicidal acts involve means other than an antidepressant overdose. Other things being equal, the strategy of prescribing newer, non-toxic antidepressants would have at best a marginal effect on the suicide rate.

Newer antidepressants may not, however, be as efficacious in treating depression as older ones.³ In a meta-analysis selective serotonin reuptake inhibitors were significantly less efficacious than tricyclic antidepressants on the 17 item Hamilton depression rating scale, but the difference was clinically small.⁴ Of 16 trials used for pooled analysis, two showed an advantage for tricyclic antidepressants, 14 showed no difference between selective serotonin reuptake inhibitors and tricyclic antidepressants, and none showed an advantage for selective serotonin reuptake inhibitors. Since then nortriptyline has been shown to be much more efficacious than fluoxetine in elderly depressed patients.⁵

When all causes of suicide are considered some of the newer antidepressants are associated with a