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.)
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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.)
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- 4 Clarke RV, Lester D. *Suicide: closing the exits*. New York: Springer Verlag, 1989.
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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.
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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

radically altered prescribing patterns. Jick and colleagues report a ratio of dothiepin to fluoxetine of 6.3:1 (number of patients treated), whereas, for the last quarter of 1994, MediPlus data show a ratio of 1.6:1. The ratio of dothiepin to all selective serotonin reuptake inhibitors was 0.86:1, making the inhibitors the most commonly used antidepressants in Britain. Jick and colleagues report an apparent increase in risk attributed to fluoxetine, which, in the light of the greatly increased prescribing of selective serotonin reuptake inhibitors since the cut off point of their data, could be important. Absence of information on comedication creates uncertainties, since many patients would have been taking several drugs. MediPlus data confirm that sleep disturbances are common in depressed patients and that benzodiazepines are commonly prescribed to such patients: of 57 000 patients taking antidepressants, 28% were also prescribed either temazepam or diazepam. The earlier data should be reassessed in the light of prevailing prescribing patterns.

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Authors' reply

EDITOR,—Our study was a descriptive study providing estimates of the risk of fatal suicide specific to certain antidepressant drugs. There was no a priori hypothesis that the results would reflect either inefficacy or an adverse reaction to these drugs.

Secondly, the comparisons in our study were between different antidepressant drugs, not between patients who had never attempted suicide and those who had previously unsuccessfully attempted suicide. No comparison was made between subjects who had successfully committed suicide and a group who had never attempted it. A history of prior suicidality was evaluated as a risk factor for fatal suicide in our study (see table V). Thus the paper gives the frequency of suicidal behaviour in subjects who did not commit suicide (as well as those who did).

Thirdly, a change in prescribing frequencies of the study drugs itself would not change the primary results.

Finally, the results in our study relate to data available to "only" February 1993 because a study of this type requires considerable time to organise and analyse the data, write a manuscript, and have it published. There is little reason to think that the results for the period since February 1993 would be materially different.

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Ultrasound treatment for pressure ulcers

EDITOR,—Gerben ter Riet and colleagues report a double blind randomised trial of ultrasound treatment and placebo in 88 patients with pressure ulcers; they found no significant differences between the treatments.¹ They also indicate that a tentative suggestion made by McDiarmid *et al* after a similar trial in 44 patients some 10 years ago, in relation to the differential efficacy of ultrasound treatment (US) in infected ulcers, was not substan-

tiated.² Both these findings come as no surprise in view of the recommendations by McDiarmid *et al* relating to the size of any future confirmatory trials. They stated:

In designing the double-blind study, it was anticipated that ultrasound would double the healing rate of pressure sores. It was also assumed that patient recruitment would be sufficient to detect such a difference with reasonable statistical power. In the event, the therapeutic effect of US on all the patients taken together appears to be marginal although it is important to note that our study does not rule out a doubling of the healing rate of US over the placebo.

Whether the difference here observed is evidence of a real therapeutic effect of US or just chance variation can only be settled by a prospective randomised trial involving many hundreds of patients. For example, if the median healing time is in fact reduced by US from approximately five to four weeks (values consistent with our results and yet clinically worthwhile) then with a two-sided test at 5% and power of 90%, this would require approximately 850 patients to be recruited to the trial. Our experience is that patient losses may be as much as 50% so that planned recruitment to such a trial should be in the order of 1300 patients. We believe, however, that such a trial would justify itself on the basis of the potential impact its result could make on the physiotherapeutic management of pressure sores.²

In view of this it is clear that ter Riet and colleagues' trial was far too small to test reliably the value of ultrasound in healing pressure ulcers. For such a common condition what is needed is a large, pragmatic multicentre (multinational) double blind trial comparing ultrasound treatment (as practised for pressure ulcers by the individual centres) with placebo. Large pragmatic trials are now common in cancer and other diseases.³ They are the only means to answer important questions such as those posed here.

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- 1 Ter Riet G, Kessels AGH, Knipschild P. Randomised clinical trial of ultrasound treatment for pressure ulcers. *BMJ* 1995; 310:1040-1. (22 April.)
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Guidelines on appropriate indications for upper gastrointestinal endoscopy

EDITOR,—A T R Axon and colleagues review the indications for upper gastrointestinal endoscopy and discuss the serological diagnosis of *Helicobacter pylori* infection in patients over 45 with dyspepsia.¹ They state that serology tests are available in most hospitals. We believe, however, that such tests are not widely available, and we therefore conducted a telephone survey of 65 British microbiology laboratories serving hospitals with 500 beds or more. We asked whether a routine serology service for *H pylori* was currently offered, whether serum samples were sent elsewhere if a service was not available, and whether *H pylori* was routinely cultured.

Most (49/65 (75%)) of the laboratories contacted did not themselves offer a serology service for the diagnosis of *H pylori* infection. Thirty five of the 49 laboratories (71%) did, however, send serum samples elsewhere. Fourteen of the 65 laboratories (22%) neither provided a routine serology service for *H pylori* nor sent samples elsewhere. Twenty eight of the laboratories (43%) cultured *H pylori*, most of them processing few routine specimens. Culture and serology of *H pylori* was currently performed by 11 laboratories (17%).

It can be difficult to interpret the results obtained by other laboratories, particularly in

serology assays where cut off values can be shifted to alter test sensitivities and specificities. Diagnostic tests for *H pylori* should be validated against the population for which they are to be used as their predictive values depend on the prevalence of infection in the target population. A further complication is the large number of serology kits that are commercially available. For example, we are currently assessing the accuracy of nine such kits in diagnosing *H pylori* infection in 100 patients presenting with dyspepsia to general practitioners.

Microbiologists seem to have been slow to take up the cause of *H pylori* as a significant gastric pathogen. This may reflect the financial pressures on diagnostic laboratories that conflict with the need for new tests, and indeed such concerns were frequently expressed in our survey. We understand that most laboratories offering a reference serology service for *H pylori* currently do so free of charge, but this is unlikely to continue. Several laboratories reported that, although they used to culture gastric biopsy specimens for *H pylori*, such specimens are now rare, presumably as the interest in rapid urease based tests and indeed in non-invasive diagnostic methods such as serology and urea breath testing has increased. We conclude that, although serology for *H pylori* is available through reference facilities, it is not widely practised. Many microbiology laboratories will probably start to offer new diagnostic serology services in the near future. Tests should be validated on the populations for which they are intended so that decisions about treatment and further investigations can be made with accuracy.

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- 1 Axon ATR, Bell GD, Jones RH, Quine MA, McCloy RF. Guidelines on appropriate indications for upper gastrointestinal endoscopy. *BMJ* 1995;310:853-6. (1 April.)

Upper gastrointestinal endoscopy

EDITOR,—The editorial by Roger Jones¹ and the guidelines for referral for endoscopy² both suggest that endoscopy early in the management of dyspepsia is more cost effective than empirical treatment, and an article by Bytzer *et al* is quoted in support of this.³ As pointed out in the guidelines, Bytzer's article disagreed with an Australian study which showed no cost or clinical advantage.⁴ In Bytzer's paper, only patients with peptic ulcer or reflux oesophagitis who had had endoscopy were given H₂ blockers.

In the real world, however, patients with no clear disease on endoscopy continue to use acid suppressants, although at a lower level,⁵ and up to 20% of patients given treatment to eradicate disease related to *Helicobacter pylori* continue to take acid suppressants.⁶ Not surprisingly in Bytzer's paper, the use of antacids by patients who had endoscopy early and were perhaps denied H₂ blockers by the protocol was greater than that in those treated without endoscopy. This artificially decreased the costs in the group that had endoscopy compared with the group treated empirically. The costs of drug treatment were also inappropriately important in the overall costing of care since the most expensive of the H₂ blockers was chosen as the study drug. No sensitivity analysis of any kind was attempted.

While the early use of endoscopy may be the most cost effective means of managing dyspepsia, particularly when identification and eradication of