

## Do selective serotonin reuptake inhibitors cause suicide?

### Risk of suicide should be assessed for whole class of antidepressants

EDITOR—Gunnell et al's report on suicide risk with selective serotonin reuptake inhibitors (SSRIs) raises several issues.<sup>1</sup>

Firstly, clinicians have observed that the first weeks of treatment of severe depression with an antidepressant are accompanied by a higher risk of suicide because of a drug induced motor disinhibition that is not yet accompanied by mood improvement.<sup>2</sup>

Secondly, the authors' finding of a trend towards a protective effect of SSRIs against suicidal thoughts (odds ratio 0.77) compared with a trend towards an increased risk of self harm (odds ratio 1.57) is paradoxical.

More surprising is the heterogeneity of results among SSRIs. Why would sertraline show a protective effect for suicidal thoughts and simultaneously increase the risk of self harm? The risk difference between citalopram and its active S-enantiomer, escitalopram, is also strange. No strong biological rationale can explain such heterogeneity among drugs with the same mechanism of action.

Thirdly, the authors mention that the Medicine and Healthcare products Regulatory Agency found little evidence for a risk difference between SSRIs and the other antidepressants. The two accompanying papers show that the suicidal risk seems similar for serotonergic and tricyclic antidepressants.<sup>3,4</sup> The risk of suicide must be assessed for the whole class of antidepressants.

The next stage would be to measure the risk of suicide according to the time since starting an antidepressant. Initially, the risks are higher than the benefits. To confirm old clinical observations by evidence based methods would be interesting and useful.

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Competing interests: None declared.

meta-analysis of drug company from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. *BMJ* 2005;330:385. (19 February.)

2 Fabre J. *Thérapeutique médicale*. Paris: Flammarion, 1983:256.

3 Fergusson D, Doucette S, Cranley Glass K, Shapiro S, Healy D, Hebert P, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005;330:396. (19 February.)

4 Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. *BMJ* 2005;330:389. (19 February.)

### Figures look doubtful

EDITOR—Gunnell et al offer figures for suicide with selective serotonin reuptake inhibitors (SSRIs).<sup>1</sup> However, in the expert

working group's report on SSRIs,<sup>2</sup> the table for citalopram indicates no suicide in the placebo group. Data on paroxetine are not available from the report, but prior submissions indicate four suicides with paroxetine (CSM Expert Working Group on the Safety of SSRIs, unpublished data, 2003). Gunnell et al note three suicides in the placebo group during the withdrawal phase, but a 1991 review of the safety of paroxetine does

not indicate that these happened in the withdrawal phase of placebo controlled trials.<sup>3</sup> If Gunnell et al are relying on a company submission these figures must be in some doubt.

Twelve suicides may have occurred in 23 804 patients taking SSRIs and six in 17 022 taking placebo, an odds ratio of 1.43; or possibly 12 suicides with SSRIs and three with placebo, an odds ratio of 2.86. Leaving paroxetine out, the figures become eight suicides in 15 323 patients taking SSRIs and three in 11 214 patients taking placebo, an odds ratio of 1.96. Adding in venlafaxine and mirtazapine gives 16 suicides in 23 885 patients taking antidepressant and three in 14 564 taking placebo, an odds ratio of 3.1.

If antidepressants reduce the risk of suicide in some patients an odds ratio of 1.0 for suicide points to a clear risk. A randomised controlled trial with a challenge-dechallenge design and a rating scale sensitive to suicidal ideation might need less than 100 patients to firm up on any risk of induced suicidality. Eli Lilly designed such a trial in conjunction

with the US Food and Drug Administration in 1990.

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1 Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. *BMJ* 2005;330:385. (19 February.)

2 Report of the CSM expert working group on the safety of selective serotonin reuptake inhibitor antidepressants. [www.mhra.gov.uk/news/2004/SSRIfinal.pdf](http://www.mhra.gov.uk/news/2004/SSRIfinal.pdf) (accessed 24 Apr 2005).

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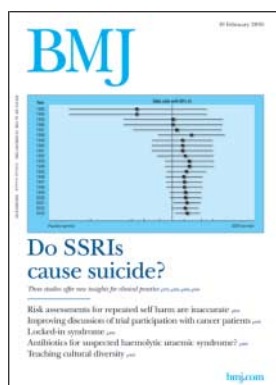
### Authors' reply to Curtin and Schulz, and Healy

EDITOR—We agree with Curtin and Schulz that drug induced motor disinhibition before mood improvement is a possible explanation for an excess of suicidal behaviour in the early weeks of antidepressant treatment.<sup>1,2</sup>

Regarding their second point, we caution against over-interpreting differences in the pooled odds ratios for self harm and suicidal thoughts or the odds ratios for different selective serotonin reuptake inhibitors (SSRIs) in relation to the same end points. Odds ratios are estimated from a small number of events, and confidence intervals overlap.

Lastly, we agree that there is little evidence for a difference in risk between different classes of antidepressant.<sup>3-5</sup>

Healy is concerned about two of the numbers in our meta-analysis. We confirm that the expert working group's report included one suicide among patients treated with placebo in placebo controlled trials of citalopram for depression (table 7.16, page 84).<sup>5</sup> Likewise data on paroxetine suicides were reported (section 7.2.1, page 74).<sup>5</sup> As we said in our paper, three of the four suicides in the placebo controlled trials of paroxetine (all in the placebo arm) occurred in the period after treatment. We therefore carried out sensitivity analysis to assess the effect on the pooled odds ratio of excluding these deaths (plus the suicide after treatment with escitalopram). This showed an increase in the odds ratio for suicide to 1.24. Healy's odds ratios are not calculated by using meta-analytic approaches for pooling data for



1 Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults:

each SSRI and so are not directly comparable with our figures.

We communicated Healy's concern with the paroxetine suicide data to the Medicines and Healthcare products Regulatory Agency (MHRA). In further consultation with the licence holder, the agency confirms that the four suicides in adult placebo controlled randomised trials of paroxetine were as described above (MHRA, personal communication, 2005).

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- 5 *Report of the CSM expert working group on the safety of selective serotonin reuptake inhibitor antidepressants.* www.mhra.gov.uk/news/2004/SSRIfinal.pdf (accessed 24 Apr 2005).

### Discrediting old drugs may be useful in marketing new ones

EDITOR—Fergusson et al report the association between suicide attempts and use of selective serotonin reuptake inhibitors (SSRIs).<sup>1</sup> A causal link between use of an SSRI and self harm would have drastic clinical implications for health services. The extra monitoring might make using antidepressants wholly impractical in a risk averse service.

The reported incidence of self harm in these studies, with estimates of 0.05-0.001%, is remarkably low. Even during a short trial, such a low incidence among patients with severe depression is not credible. The surely unique finding that rates of fatal and non-fatal self harm are identical among placebo treated patients further emphasises how unsustainable these reported figures must be. It is perhaps unsurprising that in studies designed to evaluate not self harm but efficacy, acts of self harm will be under-reported.

Under-reporting is likely to be more common among placebo treated patients. Although the methods of self harm are not stated, overdose of trial tablets might

account for several of these reports. The trial treatments are unequal since SSRIs will cause physical effects (gastrointestinal disturbance) that might prompt attendance at an emergency department. Placebo should provoke no such reaction and thus less need to report such an act of self harm.

Such data have not emerged to a barrage of opprobrium from the pharmaceutical industry. Although popular and endorsed in recent guidelines from the National Institute for Clinical Excellence,<sup>2</sup> SSRIs no longer have novelty value and are rapidly losing their patents. Data that discredit such old drugs may serve well in marketing the new generation of antidepressants.

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- 1 Fergusson D, Doucette S, Cranley Glass K, Shapiro S, Healy D, Hebert P, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005;330:396. (19 February.)
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### Let's keep it in perspective

EDITOR—The news media's preoccupation with whether antidepressants provoke suicidal behaviour has generated apprehension in the general public, and clinicians increasingly see patients resistant to taking selective serotonin reuptake inhibitors (SSRIs) even though they might benefit. The meta-analysis by Fergusson et al reported an excess of suicidal attempts with SSRIs *v* placebo and, initially, an alarming sevenfold odds ratio for fatalities compared with tricyclic antidepressants [subsequently corrected to 1.08 (0.28 to 4.09), see correction 19 March, p 653].<sup>1</sup>

A statistical excess of suicidal attempts in studies of SSRIs *v* placebo has been previously reported and was reasonably explained in the accompanying editorial by Cipriani et al.<sup>2,3</sup> However, the whole debate loses sight of the fact that the underlying trials were never designed to assess suicidality as an outcome but to satisfy regulatory agencies about efficacy. Retrospective counts of incidents of deliberate self harm or attempted suicide are extremely unreliable in such studies; fatalities obviously less so (but no excess has surfaced among these). The randomisation process in smaller trials may be questioned, and heterogeneity could have precluded some of the trials in the current meta-analysis. Prospective studies with suicidality as the outcome variable are needed to lay such issues to rest, but these have rarely been done, for valid reasons.<sup>4</sup>

In any case, odds ratios (or other ratios) alone do not give an indication of absolute risk: the number needed to harm (NNH)

should also be examined. In the current meta-analysis, an NNH of 708 compares quite favourably with others in medicine—for example, 179 in the CAPRIE trial (comparing clopidogrel with aspirin for stroke patients).<sup>5</sup>

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- 1 Fergusson D, Doucette S, Cranley Glass K, Shapiro S, Healy D, Hebert P, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005;330:396. (19 February.)
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- 3 Cipriani A, Barbui C, Geddes J. Suicide, depression, and antidepressants. *BMJ* 2005;330:373-4. (19 February.)
- 4 Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo-controlled randomized controlled trials submitted to the MHRA's safety review. *BMJ* 2005;330:385-8. (19 February.)
- 5 CAPRIE Steering Committee. A randomized blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events. *Lancet* 1996;348:1329-39.

### Data seem to be incorrect

EDITOR—Fergusson et al report that the risk of suicide attempts is significantly greater for patients enrolled in short term randomised controlled trials of selective serotonin reuptake inhibitors (SSRIs) than with placebo (odds ratio 2.28,  $P < 0.02$ ) and other interventions (not including tricyclics) (odds ratio 1.94).<sup>1</sup> They are also one of the few groups to report that completed suicides (fatal attempts) were also higher with SSRIs than tricyclics (odds ratio 7.27 [corrected to 1.08 (0.28 to 4.09), see correction, 19 March, p 653]). This seems to have led Cipriani et al to say that there is almost a double risk of fatal and non-fatal risk of suicide for people taking SSRIs.<sup>2</sup>

An increased risk of fatal overdoses when using SSRIs is hard to understand, particularly when the comparison is tricyclics, given their acknowledged toxicity in overdose.<sup>3-5</sup> I therefore rechecked the odds ratios from the data given by Fergusson et al and found most of them to be incorrect.

For example, they say that the odds ratio of suicide attempts in SSRIs compared with others is 1.94; but with 27 SSRI cases out of 4130 treated patients and 18 control cases out of 4233 treated patients the odds ratio is 1.54 (95% confidence interval 0.85 to 2.8)—that is, non-significant. Changing the denominator to 8856 and 9059 (all trials) makes no difference to the result.

Similarly, Fergusson et al say that the odds ratio for non-fatal attempts was 2.25 whereas I calculate it at 1.89 (0.96 to 3.73), again non-significant. Perhaps most incomprehensibly regarding the odds of com-

pleted suicide and tricyclics, the number of SSRI cases is five and that of tricyclic antidepressant cases is four—a non-significant difference.

In conclusion, either most of the raw data printed in table 1 are wrong or one of us has miscalculated dramatically.

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- 1 Fergusson D, Doucette S, Cranley Glass K, Shapiro S, Healy D, Hebert P, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005;330:396. (19 February)
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**Authors' reply to Jones, Sakinofsky and Streiner, and Mitchell**

EDITOR—The low rates of attempted suicide may be the result of several factors. Most studies did not enrol patients at immediate risk of suicide, and 59% of studies (414/702) were conducted in clinical indications other than major depression. The greatest contributing factors may be the under-reporting and non-reporting of events. Of the 702 trials, 345 did not provide documentation on suicide attempts.

Given the seriousness of attempted suicide, the expectation that patients in trials be well monitored, and a well documented possible association between treatment with selective serotonin reuptake inhibitors (SSRIs) and suicidality, it is disturbing that fatal and non-fatal suicide attempts were not apparently better reported. We have no empirical evidence that under-reporting may be differential because of side effects, prompting closer external monitoring of patients taking SSRIs. Good clinical trial management dictates that blinded investigators monitor all patients for all serious adverse events.

We agree that most trials evaluated were not intended to assess suicidality and strongly advocated that large clinical trials with clinically meaningful outcomes are needed to help clinicians and regulators. Given that SSRIs reduce depression and depression is associated with suicidality, we are surprised that trials assessing the effectiveness of SSRIs in reducing suicidality have not been conducted. An appropriately designed, randomised controlled trial along with validated measures of assessing suicidality would not require many patients to examine, safely, any risk and might enable antidepressants to be used more effectively and safely. Such a trial and rating scale were designed by Eli Lilly with the Food and Drug Administration in 1991 (details forwarded on request).

Ignoring individual trials and calculating summary statistics from lumped data, as Mitchell has done, is an incorrect approach to meta-analysis. Nowhere in our Methods section do we state that we calculated odds ratios from the aggregated data. Instead, we conducted meta-analyses of randomised controlled trials using Peto's method for calculating odds ratios of rare event data. Failing to preserve the randomisation of subjects at the trial level introduces bias and confounding.<sup>1</sup> Furthermore, simply calculating odds ratios from aggregated data fails to account for the influence of chance in small trials. By weighting each study by its precision, smaller trials have less influence than larger trials.

Given the enormous number of SSRIs prescribed, we maintain that a number needed to harm as large as 684 represents a public health concern. For every 1 million prescriptions, this translates into more than 1450 excess suicide attempts compared with those receiving placebo.

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**Suicide rate of 15% in editorial is misleading**

EDITOR—Cipriani et al in their editorial make many sound points about the risks and benefits of antidepressants.<sup>1</sup> However, they say that up to 15% of patients with unipolar depression eventually commit suicide. This implies that 15% is a reasonable estimate, rather than a gross overestimate based on very unrepresentative samples.

How many casual readers will be misled by this statement, which reinforces a stubbornly persistent myth?

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1 Cipriani A, Barbui C, Geddes JR. Suicide, depression, and antidepressants. *BMJ* 2005;330:373-4. (19 February)

**Authors' reply to Raven**

EDITOR—Depressed people are at increased risk of suicide, and our aim was to draw attention to the clinical severity of the problem, focusing on the real clinical dilemmas. Accurate estimation of the risk of suicide in depressed people is a crucial clinical issue. Research has been trying to measure this phenomenon for more than 30 years, and contrasting figures have been reported.<sup>1-3</sup> The true suicide risk for the average patient remains uncertain.<sup>4</sup> In our editorial we used the sentence "up to 15% of patients with unipolar depression eventually commit suicide" to emphasise the need to take this outcome very seriously, and we cited a paper by Davies et al to acknowledge how uncertain the exact risk remains.<sup>5</sup>

Additionally, we wanted to highlight an apparent existing paradox in the role of antidepressants in the treatment of depression. Instead of debating which antidepressants are more effective in reducing the risk of suicide by treating the depressive symptoms effectively, much current literature focuses on which antidepressants are less dangerous in causing suicide as an unwanted effect of treatment. This paradox indicates that further research is urgently needed to shed light on these issues.

In the meantime, doctors need to keep up to date with emerging research findings,<sup>1-3</sup> bearing in mind that untreated or inadequately treated individuals with moderate to severe depression are at increased risk of suicide.

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 Additional references w1-w3 are on [bmj.com](http://bmj.com)

### Antidepressant prescribing to children and adolescents by GPs has fallen since CSM advice

EDITOR—The decline in routine prescribing of antidepressants in children and adolescents expected by Cipriani et al has already started.<sup>1</sup> We analysed antidepressant prescribing by general practitioners between 1 January 2000 and 31 December 2004 using the IMS Disease Analyzer-Mediplus database to examine the effects of the UK Committee on Safety of Medicines' advice on antidepressant prevalence.<sup>2,3</sup>

Antidepressant use increased between 2000 and 2002 (5.4 per 1000 to 6.6/1000); the prescription of selective serotonin reuptake inhibitors (SSRIs) and venlafaxine rose. Between 2002 and 2004 antidepressant prevalence decreased (6.6/1000 to 5.7/1000). The use of the withdrawn antidepressants (citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, and venlafaxine) dropped by a third (3.1/1000 v 2.0/1000), but there was no change in fluoxetine prevalence (2.1/1000 v 2.3/1000). The use of tricyclic antidepressants declined (2.0/1000 v 1.7/1000;  $P=0.03$ ).

Since 2003 fewer children and adolescents have been prescribed antidepressants in primary care, particularly the withdrawn drugs. However, the use of fluoxetine and non-selective SSRIs has not risen, implying that they are not used as alternative treatments.

Fewer prescriptions may be issued for mild depression, or patients and their parents are more aware, and therefore more cautious, about antidepressant treatment. Also, clinicians may choose psychotherapies, such as cognitive behaviour therapy, over antidepressants.

New referrals to child and adolescent mental health services need to be measured for health service planning. Further research into the integrated management of depression in childhood and adolescence is urgently required so that adequate infrastructure and resources can be provided.

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- Committee on Safety of Medicines. Selective serotonin reuptake inhibitors (SSRIs): overview of regulatory status and CSM advice relating to major depressive disorder (MDD) in children and adolescents including a summary of available safety and efficacy data. <http://>

[medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/ssrioverview\\_101203.htm](http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/ssrioverview_101203.htm) (accessed 15 Feb 2005).

### Attributable lung cancer risk from radon in homes may be low

EDITOR—Darby et al provide compelling evidence that indoor radon is an important contributor to the risk of lung cancer.<sup>1</sup> However, the derived estimate of radon attributable lung cancers may have a low bias.

The authors estimate an increase in lung cancer risk of 16% for each incremental 100 Bq/m<sup>3</sup> of radon from a pooling of the European residential case-control studies. They then estimate that radon may contribute to 9% of all lung cancers in those countries on the basis of an estimated average radon concentration of 59 Bq/m<sup>3</sup> for 29 European countries. However, the relative risk per Bq/m<sup>3</sup> was determined in each study for an exposure window of five to 35 years before ascertainment of the disease.

Typically, lung cancer will occur after the age of 55, so exposures received during childhood and young adulthood are not included. This would not be a problem if exposures occurring more than 35 years previously did not contribute appreciably to lung cancer risk. However, although the BEIR VI models do incorporate a fall-off in risk with time, the projected risk from childhood and young adult exposures are still about the same as for the population as a whole.<sup>2,3</sup> As a result, more than 30% of the radon contribution to the population risk would be unaccounted for by the case-control studies.

This conclusion is based on model extrapolation; in reality, aside from very limited, and somewhat equivocal, data on Chinese tin miners,<sup>4</sup> no direct information is available on risks from childhood exposures to radon. Also, if radon levels before the 30 year measurement window were highly correlated with the estimated average levels during the window, the error would be reduced since the measured average exposure rate would reflect the entire lifetime, rather than just 30 years. This is unlikely to be true in practice since people are unlikely to have lived in the same houses during childhood and early adulthood as they did for the 35 years before the incidence of lung cancer.

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- Darby S, Hill D, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ* 2005;330:223-6. (29 January.)
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4 Xuan XZ, Lubin JH, Li JY, Li-Fen Y, Sheng LQ, Lan Y, et al. A cohort study in southern China of tin miners exposed to radon and radon decay products. *Health Phys* 1993; 64:120-131.

### Many patients may not understand consent forms

EDITOR—McKinney et al highlight an important issue—namely, the difficulty of obtaining truly informed consent.<sup>1</sup> This is a process that most surgeons engage in every day. The current requirement for informed consent is backed by a written record of the consent process in the form of a standard consent form that has been distributed by the Department of Health.<sup>2</sup>

Thousands of these forms are signed daily, but do we as doctors ever stop to consider how much of the form is read by patients and for those who do read it, how much of it is understood? Standard readability measurements can be used to assess readability, the Flesch readability ease score being one of the most validated. A document scoring 65 or above is considered to be readable for most adults. I found that the score for the entire text of the standard UK consent form is 45.1 and that the "Statement of patient" section, which details important patient concessions, is not much better at 48.9. These scores correspond to a "difficult college" level of literacy to understand the document.

The Office for National Statistics published data in 1996 that indicate that nearly half of the UK adult population between the ages of 16 and 65 have levels of literacy low enough to significantly interfere with daily work tasks.<sup>3</sup> As clinicians and health communicators, we must either shoulder the additional burden of translating the current consent form into understandable language for a proportion of our patients or we should consider using another, more patient friendly form.

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