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BMJ 2004;329:34-38
doi:10.1136/bmj.329.7456.34

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Antidepressants and suicide: what is the balance of benefit and harm

David Gunnell, Deborah Ashby

Prescribing of antidepressants has increased greatly in England and elsewhere in recent years. 12 This increase has coincided with a fall in rates of suicide, leading some researchers to suggest a causal association. 13-15 Meanwhile, others are concerned that antidepressants may precipitate suicidal behaviour. 7 A recent review of evidence from paediatric trials by the Committee on Safety of Medicines in Britain led to most selective serotonin re-uptake inhibitors (SSRIs) being contraindicated in people aged younger than 18. 12

Is increased prescribing linked to reduced suicide rates?

SSRIs and tricyclic antidepressants account for over 90% of antidepressant prescribing in Britain. Systematic reviews confirm that both these classes of antidepressant are effective in adults, 16 although SSRIs are better tolerated by patients. 11 The effectiveness of antidepressants in childhood and adolescence is less clear. 12

As depression is the main psychiatric condition leading to suicide, it seems reasonable to infer that rises in antidepressant prescribing, which indicate improved management of depression, should have a beneficial effect on suicide rates. Indeed, an intervention to improve general practitioners’ management of depression in a Swedish community resulted in increased antidepressant prescribing and a short term reduction in suicide. 17

Summary points

Concern is growing that serotonin reuptake inhibitors (SSRIs) may precipitate suicidal behaviour, especially in children. Reassuringly, although antidepressant prescribing in Britain has more than doubled in the past 15 years, population suicide rates have fallen. If the risks of SSRIs associated suicidal behaviour seen in children were to apply to suicide in adults, the number of “antidepressant induced” suicides would be small enough to be masked by currently favourable suicide trends. Long term studies are required to assess the risks and benefits to population health of recent large scale rises in antidepressant prescribing.

Surprisingly, direct evidence that antidepressants prevent suicide is hard to find. A meta-analysis of data on the SSRIs fluoxetine, funded by its manufacturer, found no evidence that suicidal acts were less frequent among adults taking antidepressants; the pooled incidences were 0.3% for fluoxetine, 0.2% for placebo, and 0.4% for tricyclics. 16 In the most comprehensive synthesis of data from randomised trials,
Khan and colleagues found no evidence of a beneficial effect of antidepressants on suicide. These findings are difficult to interpret as this was not a formal meta-analysis and relative risks were not derived separately for each trial on an intention to treat basis.

Suicide is rare, even among people with depression. Thus, most clinical trials have insufficient power to provide clear evidence on the effect of antidepressants on suicide.

Time trends
In the absence of clear evidence from clinical trials, researchers have investigated whether rises in antidepressant prescribing are associated with reductions in population suicide rates. With some exceptions, such studies conclude that recent rises in prescribing have contributed to falls in suicides. Interpretation of these findings is not straightforward. A range of factors influence population suicide rates. It is therefore challenging to distinguish the discrete effects of increased antidepressant prescribing from changes in other risk factors.

Furthermore, declining overall suicide trends may mask rises in some age and sex groups. In Australia, recent rises in antidepressant prescribing were associated with falls in suicide among some age and sex groups but increases in others. In Britain, declines in suicide preceded increases in prescribing (see fig A on bmj.com) and rises in antidepressant prescribing since 1991 in different age and sex groups do not consistently coincide with clear changes in previous suicide trends (fig 1). The levelling out of suicide trends in young men is probably due to a fall in suicide by self poisoning with car exhaust because of reductions in the carbon monoxide content of exhaust gases.

Toxicity
The possible benefits of increases in SSRI prescribing are not limited to their effect on depression. Self poisoning accounts for around a quarter of suicides in England; 20% of these deaths are antidepressant overdoses. Tricyclic antidepressants are considerably more toxic in overdose than SSRIs. Consequently, it has been estimated that a switch from tricyclics to SSRIs as first line treatment for depression could prevent 300-450 overdose deaths a year through restricting access to the more toxic antidepressants.

Of note, increased SSRI prescribing has not been accompanied by a fall in use of tricyclics (fig 2).

Do antidepressants increase the risk of suicide?
Soon after the launch of fluoxetine, the most commonly prescribed SSRI, a series of reports were published suggesting worsening of depression and emergence of suicidal thoughts in some people. The issue has been hotly debated. Disentangling the evidence is problematic as much of the research is sponsored by the pharmaceutical industry. Review of data from paediatric trials of SSRIs shows that published findings present a more favourable risk-benefit profile than unpublished trials sponsored by industry.

Table 1 summarises the evidence from clinical trials on the adverse effects of SSRIs on suicidal behaviour in children, abstracted from information recently released by the Medicines and Healthcare Products Regulatory Agency. No suicides occurred in these trials. The pooled estimate of increased risk of suicidal thoughts or behaviour from these data is 1.66 (95% credibility interval 0.83 to 3.50). Interpretation of this apparent increase in risk is problematic as people taking SSRIs may be more likely to report adverse effects, perhaps because the drugs could have a
Clinical review

In addition, response to treatment may lead to reactivation among people whose depression previously prevented them from acting on suicidal impulses. Furthermore, any increased risk may be counterbalanced by a longer term reduction in suicidal behaviour; such benefits would not detected in the trials as they generally lasted 10 weeks or less, whereas the mean duration of treatment in clinical practice is three to four months.

Reassuringly, time trends for suicide (England and Wales) and non-fatal self harm (Oxford) in children and adolescents provide no consistent evidence of adverse trends paralleling increased prescribing in the 1990s, although there is some evidence of a rise in non-fatal self harm in young females. Furthermore, in the United States, recent research suggests that areas with the largest increases in antidepressant prescribing to 10-19 year olds experienced the greatest falls in suicide.

Modelling the effect

There are two reasons why an adverse effect of antidepressants on suicide risk may have been overlooked in adult clinical trials. Firstly, self harm, and fatal self harm in particular, is relatively rare, and most clinical trials lack power to detect any increased risk. Secondly, as it seems counterintuitive that treatments for depression might increase suicide risk, the possibility may not have been specifically investigated in the clinical trials. The increased risk in children may have been detected either because of the increased prevalence of suicidal thoughts and self harm in young people (giving greater power) or because the absence of beneficial effects meant that adverse effects dominated the clinical picture.

If rare adverse effects of antidepressants on suicide exist, recent large scale increases in prescribing might be expected to affect suicide trends. But, as detailed above, recent suicide trends have generally been favourable, and so it is likely either that benefits outweigh the risks in adults or that any excess risk is small. Nevertheless, antidepressants may have precipitated some suicides in susceptible individuals, and it is important to estimate the number of such deaths. Table 2 outlines a model to estimate the number of excess deaths that may have occurred in 2002 compared with 1991 as a result of their increased use in England.

The model is based on the worst case scenario that the findings in relation to non-fatal self harm in paediatric trials are applicable to suicide deaths in adults. Under the model’s assumptions (see bmj.com) an excess of 588 suicides (95% credibility interval −202 to 704) (233 men and 155 women) may have occurred in 2002 compared with 1991 as a result of increased antidepressant prescribing. This is equivalent to an annual increase of around 35 suicides since 1991 (0.8% of the roughly 4500 annual suicides in England). Such a small increase may have been masked by other favourable influences on suicide.

The credibility intervals of our estimated increase in suicides (−202 to 704) include the possibility of a null or beneficial effect of SSRIs. Furthermore, some of our model assumptions are likely to result in us overestimating possible SSRI associated suicides. Firstly, there is no evidence that the findings from the paediatric trials can be extrapolated to adults, nor indeed that the strength of associations are the same for fatal and non-fatal self harm. Furthermore, the relative risk we used in our main model is based on findings from trials generally lasting 10 weeks or less, whereas the recommended duration of treatment is six months or more. Any increased suicide risk early in treatment may be offset by longer term improvements in suicide risk.

Secondly, we will have overestimated person time at risk because not all dispensed prescriptions are used and we have not taken account of the fact that (any) antidepressant associated increased risk of suicide may be concentrated in the early weeks of treatment. A sizeable proportion of people prescribed the drugs are long term users or have been taking antidepressants for two months or more and may therefore not be at risk of side effects.

Table 1 Risk of suicidal behaviour associated with use of SSRIs to treat depression in children and adolescents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration of trial(s) (weeks)</th>
<th>Adverse outcomes (drug v placebo)*</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>8</td>
<td>Suicide attempts: 2.4% (6/249) v 1.9% (4/209)</td>
<td>1.3 (0.4 to 4.4)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>10</td>
<td>Suicide related events (includes suicidal thoughts): 2.7% (5/189) v placebo: 1.1% (2/184)</td>
<td>2.4 (0.5 to 12.4)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>8-10</td>
<td>Self harm: 8.0% (17/213) v 4.9% (10/205)</td>
<td>1.6 (0.8 to 3.5)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>8-12</td>
<td>Possibly related to suicidality*: 3.7% (14/378) v 2.5% (7/266)</td>
<td>1.5 (0.6 to 3.7)</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td>—</td>
<td>—</td>
<td>1.66 (0.83 to 3.5)†</td>
</tr>
</tbody>
</table>

*Risks in relation to specific drugs were pooled from up to three trials. When data were presented separately we focused on risk in relation to self harm rather than suicidal thoughts.
†Pooled estimates derived from bayesian random effects model.
Table 2 Model of possible excess suicides in 2002 compared to 1991 as a result of increased antidepressant prescribing (assumes findings from paediatric trials apply to adults and additional assumptions listed in text)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of extra antidepressant prescriptions issued in England in 2002 compared with 1991 (Department of Health)†</td>
<td>17 386 000</td>
<td>7 596 000</td>
<td>9 790 000</td>
</tr>
<tr>
<td>Additional persons exposed to antidepressants in 2002 compared to 1991</td>
<td>1 381 000</td>
<td>460 000</td>
<td>921 000</td>
</tr>
<tr>
<td>Suicide rate in primary care treated depression (based on mean one year follow up)¶</td>
<td>85/100 000/year</td>
<td>127.5/100 000/year</td>
<td>42.5/100 000/year</td>
</tr>
<tr>
<td>No of suicides among people receiving antidepressants§</td>
<td>586</td>
<td>391</td>
<td></td>
</tr>
<tr>
<td>No of excess suicides¶¶</td>
<td>586/(586/1.66)=233</td>
<td>391/(391/1.66)=155</td>
<td></td>
</tr>
</tbody>
</table>

†Assumes mean duration of antidepressant prescription is 29 days and all dispensed prescriptions are taken in their entirety by patients (No of extra prescriptions=29/365).
‡Assuming ratio of male/female suicide rates among people taking antidepressants is the same as that for general population suicide rates: 3.1. This is in keeping with the relative risk of suicide of 2.8 in males receiving antidepressants compared with females in Jick et al.5
$ Additional person years of prescriptions×annual suicide rate.
¶¶ Assuming relative risk associated with antidepressant prescribing is 1.66 (see table 1).

Lastly, we assumed that suicide rates among those receiving antidepressants in 2002 are similar to those in the late 1980s and early 1990s. Recent increases in prescribing are likely to have occurred among people with less severe depressive illness and therefore a lower absolute suicide risk. The balance of risk and benefits may be different in this patient group. Our estimate of suicide rates among those treated with antidepressants is, however, some five times lower than that reported in one study. A sensitivity analysis of our model assumptions is presented on bmj.com.

Conclusions

There is no strong evidence that increases in antidepressant prescribing lie behind recent reductions in population suicides. Furthermore, data from paediatric trials suggest that SSRIs are associated with an increased risk of suicidal behaviour and most SSRIs seem to be ineffective for childhood depression. However, current concerns about the safety of SSRIs come from clinical trials both of too short duration (<10 weeks) to identify longer term beneficial effects and are carried out in children and adolescents, among whom suicide is rare.

From the population perspective, the balance sheet of risks and benefits of SSRIs is unclear. Any antidepressant induced suicides may be offset by the beneficial effects of antidepressants on depression and long term suicide risk associated with untreated depression. The low toxicity of SSRIs in overdose will prevent some suicides. The balance of risks and benefits may vary depending on an individual's underlying suicide risk. For patients with conditions that have a high risk of suicide, such as severe depression, the risk-benefit balance may be more favourable than for patients with conditions such as anxiety and mild depression, in which suicide is rare. It is in these lower risk conditions, however, that much of the recent rise in prescribing has probably occurred.

Depression is a common and disabling condition, and so the safety of drugs used in its management is crucial. Future trials of antidepressants should be of sufficient duration to detect longer term benefits of this class of drug and balance these against possible risks. They should also systematically collect data on suicidal thoughts and behaviour. Long term studies are required to assess the effect on population health of recent rises in antidepressant prescribing.

We thank Ian Weller and George Davey Smith for critical comments on the paper, IMS Health for the age specific prescribing data, the Department of Health for prescribing data, Lesley Wise for critical comments and helpful discussions on our model, and Shahrul Mt Isa, for help with calculating the confidence intervals.

Contributors and sources: DG has a longstanding research interest in the epidemiology and prevention of suicide. DA has a longstanding research interest in drug safety and bayesian modelling. The idea for the paper arose from their joint work on the Medicines and Healthcare Products Regulatory Agency's Expert Working Group on SSRIs. DG wrote the first draft of the article and undertook literature reviews; DA performed the statistical modelling; both authors contributed to the final content of the paper and will act as guarantors.

Competing interests: DG and DA are members of the Medicines and Healthcare Products Regulatory Agency's expert working group on the safety of SSRIs and DA is a member of the Committee on Safety of Medicines. We act as independent advisers, receiving travel expenses and a small fee for attending meetings and reading materials in preparation for the meeting. DA has spoken on the methodology of adverse drugs reactions in HIV at a scientific meeting attended by several pharmaceutical companies, and sponsored by GlaxoSmithKline. An honorarium was paid to her department.

Interactive case report

A 64 year old woman with knee pain: case outcome

Peter Tugwell, Annette M O’Connor, Nancy A Santesso

Four weeks ago (5 June, p 1362) we presented the case of Mrs Patell, who visited her doctor after reading a newspaper article about the risks of chronic use of paracetamol with alcohol intake. Although she needed the pain relief, she was reluctant to give up alcohol. Her general practitioner discussed the benefits and harms of paracetamol versus non-steroidal anti-inflammatory drugs and gave her a decision aid to help her clarify her decision (12 June, p 1425).

After discussing her completed decision aid with her general practitioner, Mrs Patell decided to continue the paracetamol up to 4000 mg/day. She has reduced her alcohol intake but feels that the small increase in her risk of liver disease associated with alcohol is still preferable to the even greater risk of bleeding with non-steroidal anti-inflammatory drugs.

This case is fictional but was developed from several real cases. It was commissioned to contribute to this special issue on harms.

bleeding with non-steroidal anti-inflammatory drugs. Mrs Patell is confident in her decision and feels that she was given enough information and guidance to allow her to make an informed, value based decision.

In this case, the doctor could not clearly recommend a treatment option to the patient. The evidence of benefits and harms was not clear, and the value the patient placed on the benefits and harms was not known. The doctor recognised that Mrs Patell was uncertain about what to do but wanted to be involved in the decision making process and used a decision aid. A Cochrane systematic review of over 30 randomised trials of decision aids provides clear answers about the efficacy of decision aids. Compared to usual care, decision aids improve patients’ knowledge of options, create realistic perceptions of the probabilities of benefits and harms, clarify personal values, enhance participation in decision making without affecting anxiety, reduce decisional conflict about the best course of action, and improve the match between what patients’ value and what they choose.

We thank George Wells and Joan Peterson for help with the calculations.

Competing interests: PT received travel and research support from pharmaceutical companies. AOC receives an unrestricted research grant from the Foundation for Informed Medical Decision Making, which has a licensing agreement with Health Dialog, a company that markets decision aids.