Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials

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Abstract

Objective To establish whether an association exists between use of selective serotonin reuptake inhibitors (SSRIs) and suicide attempts.
Design Systematic review of randomised controlled trials.
Data sources Medline and the Cochrane Collaboration's register of controlled trials (November 2004) for trials produced by the Cochrane depression, anxiety, and neurosis group.
Selection of studies Studies had to be randomised controlled trials comparing an SSRI with either placebo or an active non-SSRI control. We included clinical trials that evaluated SSRIs for any clinical condition. We excluded abstracts, crossover trials, and all trials whose follow up was less than one week.
Results Seven hundred and two trials met our inclusion criteria. A significant increase in the odds of suicide attempts (odds ratio 2.28, 95% confidence 1.14 to 4.55, number needed to treat to harm 684) was observed for patients receiving SSRIs compared with placebo. An increase in the odds ratio of suicide attempts was also observed in comparing SSRIs with therapeutic interventions other than tricyclic antidepressants (1.94, 1.06 to 3.57, 239). In the pooled analysis of SSRIs versus tricyclic antidepressants, we did not detect a difference in the odds ratio of suicide attempts (0.88, 0.54 to 1.42).
Discussion Our systematic review, which included a total of 87 650 patients, documented an association between suicide attempts and the use of SSRIs. We also observed several major methodological limitations in the published trials. A more accurate estimation of risks of suicide could be garnered from investigators fully disclosing all events.

Introduction

Selective serotonin reuptake inhibitors (SSRIs) rank among the most commonly prescribed medications in the world, in large part because they have been marketed as safe and effective in treating depression and an expanding list of additional conditions. Concerns related to safety were raised in the early 1990s, with reports describing a possible association with suicidality.[1–3] However, inferences regarding the plausibility and strength of the association have been divergent.[4–6] Because suicides and suicide attempts are rare events, the inability to document an important difference may be a function of the small number of patients in trials. Nevertheless, public health advisories concerning the use of antidepressants and suicidality have been issued.[7 8]

Given the controversy, we undertook a systematic review of all published randomised controlled trials regardless of treatment indication, to evaluate the association between suicide attempts and the use of SSRIs.

Methods

Literature search strategy

We conducted a systematic literature search to identify all randomised controlled trials of SSRIs indexed on Medline between 1967 and June 2003. We searched the Cochrane Collaboration's register of controlled trials (November 2004) (Cochrane depression, anxiety, and neurosis group) with the same strategy, and reviewed the bibliographies of three systematic reviews and identified trials to identify relevant reports. Three authors independently reviewed all citations. Each potentially relevant citation was reviewed by at least two individuals. Disagreements were resolved by consultation with a third reviewer.

Eligible studies had to be randomised controlled trials comparing an SSRI with either placebo or an active non-SSRI control, for any clinical condition. We excluded abstracts, crossover trials, and all trials whose follow up was less than one week. We abstracted information on to a standardised data abstraction form. See bmj.com for details of search strategy.

Outcomes

The primary outcome, suicide attempts, included both fatal and non-fatal acts of suicide. We documented rates of each separately. The authors had literally to use the term "suicide." The one exception was the use of the term "overdose." We made conservative assumptions to

ELPS *This is the abridged version; the full version is on bmj.com*

deal with the published reporting of non-fatal suicide attempts. If the authors explicitly reported that there were no adverse or serious adverse events we recorded that there were no fatal or non-fatal suicide attempts. If no suicide attempts were mentioned but the authors accounted for all adverse events and reasons for discontinuation we recorded zero suicide attempts. Subjects for which the authors did not indicate a reason for withdrawal or discontinuation we did not count as suicide attempts.

We documented how adverse events were reported, dropout rates, sample size, and the number of trials that did not report adverse events. We included a "not reported" category consisting of trials that did not mention adverse events or reasons for discontinuation of therapy, provided an incomplete listing of all adverse events, or did not explicitly state that no serious adverse events occurred.

Analysis

As an initial description of the risk of suicide overall and in major comparisons, we calculated the absolute risk per 1000 patients treated. To account for exposure time, we calculated the number of episodes of suicide attempts per 1000 person years of exposure by assuming a constant risk over the first year and using a weighted average of exposures.

We undertook three separate meta-analyses: SSRIs compared with placebo, with tricyclic antidepressants, and with other active forms of treatment excluding placebo and tricyclic antidepressants. Within each comparison, we tested the association between suicide attempts and the use of SSRIs by estimating summary odds ratios and 95% confidence intervals, using fixed effects models (Peto). We conducted separate meta-analyses for the number of fatal and non-fatal suicide attempts. We did not incorporate trials categorised as "not reported" into the analyses.

A priori subgroups of interest were based on age, the duration of the study follow up, proportion of women, and primary diagnosis of participants in the trials. We examined the reported partial or total funding source (funded by, compared with not funded by, the pharmaceutical industry). We also conducted a cumulative meta-analysis to evaluate the temporal sequence of evidence of effect.

Results

The literature search identified a total of 3717 citations. After exclusions, 624 met the inclusion criteria. A further 78 trials were identified from the Cochrane Collaboration register of controlled trials and the bibliographies of the three systematic reviews and of all eligible trials, giving a total of 702 trials (see bmj.com). As some trials had more than one comparison arm, the total number of comparisons exceeds the number of published trials. Of the 159 comparisons other than placebo or tricyclic antidepressants, the most common comparative treatments were moclobemide (21 trials), psychotherapy (20), maprotiline (18), and mianserin (16).

A total of 345 trials representing 36 445 patients reported the number of suicide attempts (143 in total) and were included in the analysis. Of the 345 trials reporting suicide attempts as adverse events, 64 reported at least one suicide attempt. In comparing trial characteristics between trials that reported suicide attempts and those that did not, the only significant difference was that larger trials tended not to report (χ^2 test, df = 2, P = 0.001). The overall rate of suicide attempts was 3.9 (95% confidence interval 3.3 to 4.6) per 1000 patients treated in clinical trials. When we used study duration as exposure time, we found an incidence of 18.2 suicide attempts per 1000 patient years. For the trials conducted in patients with depression, the overall rate of suicide attempts was 4.9 (95% confidence interval 4.2 to 5.6 per 1000 patients). The table provides the reported numbers of fatal and non-fatal suicide attempts.

We found a significant increase in the odds of suicide attempts (odds ratio 2.28, 1.14 to 4.55, number needed to treat to harm 684; P = 0.02) for patients receiving SSRIs compared with placebo (fig 1). Given reduced sample sizes, our ability to detect significant differences within subgroups was limited. However, all odds ratios exceeded 1.0 except for trials whose participants had a mean age of over 60 (fig 1). In comparing non-fatal suicide attempts, a significant difference overall remained (2.70, 1.22 to 5.97; P = 0.01). In comparing fatal suicide attempts, we did not detect any differences between SSRIs and placebo (0.95, 0.24 to 3.78).

In the pooled analysis of SSRIs compared with tricyclic antidepressants, we did not detect differences in the odds of suicide attempt (0.88, 0.54 to 1.42). We found no clinically or statistically important differences in any subgroup analyses. The odds ratio of non-fatal suicide attempts was 0.85 (0.51 to 1.43) and the odds ratio of fatal suicide attempts for SSRIs compared with tricyclic antidepressants was 7.27 (1.26 to 42.03).

We found an increase in the odds of suicide attempts when comparing SSRIs with therapeutic interventions other than tricyclic antidepressants (1.94, 1.06 to 3.57, number needed to treat to harm 239). Again with smaller sample sizes, we found no subgroup specific differences that reached significance. All odds ratios exceeded 1.0, except for trials in which the proportion of women exceeded 75%. The odds ratio for fatal suicide attempts was 0.59 (0.16 to 2.24) and that for non-fatal suicide attempts 2.25 (1.16 to 4.35).

Fatal and non-fatal suicide attempts in the analysed trials

	No of trials*		No of patients				No of suicide attempts					
			All trials		Trials that report		Fatal		Non-fatal		Total	
	All trials	Trials that report	SSRI	Control	SSRI	Control	SSRI	Control	SSRI	Control	SSRI	Control
SSRI *v* placebo	411	189	28 803	21 767	10 557	7856	4	3	23	6	27	9
SSRI *v* tricyclic antidepressants	220	115	12 740	11 609	6126	5401	5	4	29	31	34	35
SSRI *v* other	159	83	8856	9059	4130	4233	3	5	24	13	27	18

SSRI=selective serotonin reuptake inhibitors. *Represents the number of comparisons, as some trials had more than one comparison arm.

Patient group	SSRI No of patients	SSRI No of attempts	Placebo No of patients	Placebo No of attempts
Overall	10557	27	7856	9
Condition				
Major depression	3641	13	3243	7
Depression	1665	4	1127	1
Other conditions	5251	10	3486	1
Trial duration				
≤6 weeks	3094	8	2096	3
7+ weeks	7413	19	5710	6
Age group				
<60 years old	9798	26	7110	8
>60 years old	759	1	746	1
Sex				
<25% female	620	0	426	0
25-50% female	1706	2	1331	2
50-75% female	5731	20	4598	6
75-100% female	2178	4	1250	1
Reported funding				
Funded by pharmaceutical industry	5965	16	4647	5
Not funded by pharmaceutical industry	4592	11	3209	4

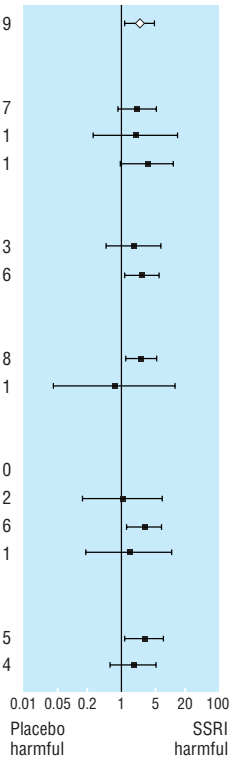

Fig 1 Fatal and non-fatal suicide attempts in SSRI trials and placebo trials

Discussion

We documented a more than twofold increase in the rate of suicide attempts in patients receiving SSRIs compared with placebo or therapeutic interventions other than tricyclic antidepressants. We documented a difference in absolute risk of 5.6 suicide attempts per 1000 patient years of SSRI exposure compared with placebo. Although small, the incremental risk remains an important population health issue because of the widespread use of SSRIs. Cumulative meta-analysis reinforces concern with the potential trend towards harm over the past several years (fig 2). It is unclear whether regulatory authorities were aware of this or not.

Possible explanations for our findings

The increase in the number of suicide attempts was not associated with a comparable increase in the risks of fatal suicide attempts. Several explanations are plausible. Estimates for patients with major depression favoured a decrease in suicides with SSRIs, whereas patients with depression and other clinical indications may have as much as an eightfold increase in the rates of suicide, thus resulting in an overall null effect. In all instances, the number of events was too small to generate sufficiently narrow confidence intervals. Alternatively, the agitation and akathasia known to occur with SSRIs may have induced more distress in patients with less severe clinical conditions and may account for the greater number of suicide attempts in patients without severe depression. Another explanation could be that treating more severely depressed patients with a higher inherent risk of suicide in a controlled environment may produce a more favourable ratio of risks to benefits. One implication from our findings is that patients with mild illness who are being treated without supervision in the community may require closer monitoring by general practitioners, family, friends, or work colleagues.

A review of published and unpublished sources documented increased rates of suicide in patients with depression when records from the Food and Drug Administration (FDA) were considered, of approximately 15.3 episodes per 1000 patients treated with SSRIs.[9] Our review noted suicide attempts at a rate of 3.9 episodes per 1000 patients. The difference in rates implies that a substantial proportion of suicide attempts have gone unreported.[5 10]

Limitations

As additional evidence of difficulties in reporting, we were unable to find documentation confirming or refuting suicide attempts in 51 205 of the 87 650 patients. We conducted a survey of a random sample of 35 (10%) of these trials. Of those responding, 22.2% of trials (n = 2) reported a suicide attempt compared with 18.6% of trials (n = 64) in our entire sample.

Only one trial (0.14%) mentioned a potential association between suicidality or any aspect of self inflicted injuries and SSRIs in their background or discussion sections. One hundred and four of the 702 trials reported adverse events that occurred in excess of a prespecified threshold of either 3%, 5%, or 10% of patients or above a certain number of patients. As a consequence, rare but lethal complications may have gone unreported or under-reported.

We also documented other important limitations. Of 493 trials that reported dropout rates, 28.7% (n = 18 217) of the 63 478 patients dropped out. In most study areas, patients who are lost to follow up tend to be less compliant, do not derive comparable

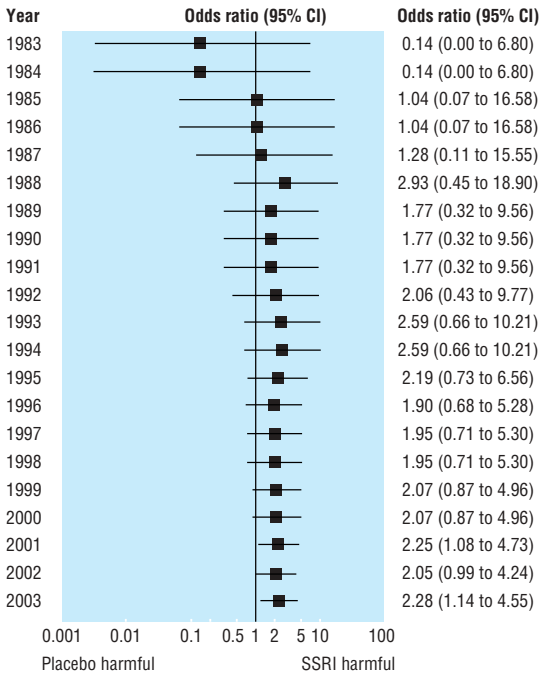

Fig 2 Cumulative meta-analysis of fatal and non-fatal suicide attempts in placebo controlled trials

benefits, and have a greater frequency of adverse outcomes compared with other patients in trials.[11] High rates of losses to follow up may therefore have hindered the ability to detect risks of suicide.

Trial size and duration of follow up are obstacles to detecting associations between SSRIs and rare adverse events. Clinical trials have focused largely on symptoms rather than long term outcomes, such as resolution of depression, prevention of relapse, and long term quality of life. In our review, 62.3% of trials (n=437) enrolled fewer than 100 patients and the mean duration of treatment and follow up in published trials was 10.8 weeks. It is therefore impossible to infer rates of long term risks and benefits of treatment, especially in relation to other therapies.

In 29 trials representing 4243 patients, investigators limited trial entry to those patients who were known to respond to and tolerate SSRIs. This would effectively diminish adverse events during the conduct of the trial. In addition, some trials enrolled patients receiving SSRIs into a placebo arm without an adequate washout period, thereby potentially attributing adverse events associated with the discontinuation of treatment to the placebo or attributing adverse events to placebo in patients who were successfully treated by SSRIs.

Conclusions

We documented an association between suicide attempts and the use of SSRIs. A more accurate estimation of the risks of suicide would be garnered from investigators fully and accurately disclosing all events. Our review also showed major limitations in the published medical literature. Doctors rely on published reports for their treatment decisions, making open and complete reporting scientifically and ethically essential.

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Competing interests: DH has had consultancies with, been a principal investigator or clinical trialist for, been a chairman or speaker at international symposia for, or been in receipt of support to attend foreign meetings from: Astra, Astra-Zeneca, Boots/Knoll, Eli Lilly, Janssen-Cilag, Lorex-Synthelabo, Lundbeck, Organon, Pharmacia & Upjohn, Pierre-Fabre, Pfizer, Rhone-Poulenc Rorer, Roche, SmithKline Beecham, Solvay, and Zeneca. DH has been an expert witness for the plaintiff in eight legal actions involving SSRIs and has been consulted on several cases of attempted suicide, suicide, and suicide-homicide after antidepressant medication, in most of which he has offered the view that the treatment was not involved. He has also been an expert witness for the defendants (the British NHS) in a large series of lysergic acid diethylamide (LSD) and electroconvulsive therapy (ECT) cases.

What is already known on this topic

Selective serotonin reuptake inhibitors (SSRIs) are a widely prescribed medication

SSRIs are used to treat an expanding list of indications

Divergent studies exist on whether SSRIs are associated with an increase in suicidal events

What this study adds

Evidence from this study supports the association between the use of SSRIs and increased risk of fatal and non-fatal suicide attempts

While the incremental risk is low, the widespread use of SSRIs makes this a population health concern

A number of major methodological limitations of the published trials may have led to an underestimate of the risk of suicide attempts

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