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Lines of Evidence on the Risks of Suicide with Selective Serotonin Reuptake Inhibitors

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Key Words

Selective serotonin reuptake inhibitors · Suicidality · Antidepressants · Depression · Risk-benefit ratios

Abstract

Background: There has been a long-standing controversy about the possibility that selective serotonin reuptake inhibitor (SSRI) antidepressants might induce suicidality in some patients. ***Methods:*** Starting from the clinical studies that gave rise to this issue, this paper reviews an unselected cohort of randomized clinical trials (RCTs), a series of meta-analyses undertaken to investigate aspects of the problem, studies in recurrent brief depressive disorders, epidemiological studies and healthy volunteer studies using SSRIs to shed light on this issue. ***Results:*** The original clinical studies produced evidence of a dose-dependent link, present on a challenge, dechallenge and rechallenge basis, between SSRIs and both agitation and suicidality. Meta-analyses of RCTs conducted around this time indicate that SSRIs may reduce suicidal ideation in some patients. These same RCTs, however, yield an excess of suicides and suicide attempts on active treatments compared with placebos. This excess also appears in the best-controlled epidemiological studies. Finally, healthy volunteer studies give indications that SSRIs may induce agitation and suicidality in some individuals. ***Conclusions:*** The data reviewed here, which indicate a possible doubling of the relative risk of both suicides and suicide attempts on SSRIs compared with older antidepressants or non-treatment, make it difficult to sustain a null hypothesis, i.e. that SSRIs do not cause problems in some individuals to whom they are given. Further studies or further access to data are indicated to establish the magnitude of any risk and the characteristics of patients who may be most at risk.

Introduction

There has been a controversy for a decade as to whether selective serotonin reuptake inhibitor (SSRI) antidepressants can trigger suicidality in vulnerable individuals. No studies designed to investigate these issues have been undertaken. This review, therefore, will cover the evidence for frequency of suicides and suicide attempts from randomized clinical trials (RCTs) of recently released antidepressants, the controlled case studies that gave rise

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to initial concerns about SSRIs, meta-analyses of efficacy studies in depression that have included data on the frequency of suicidal acts, a set of RCTs in recurrent brief depression, epidemiological studies, and a set of SSRI healthy volunteer studies. This review is focused exclusively on the data from the studies listed above and does not attempt to encompass any other reviews on this issue or neurobiological studies on possible relationships between the serotonin system and suicidality.

Controlled Case Studies

The debate regarding SSRIs and suicide started in 1990, when Teicher et al. [1] described 6 cases in which intense suicidal preoccupation emerged during fluoxetine treatment. In subsequent contributions, these authors related this problem to the generation of akathisia. They described a dose-response relationship to a problem that cleared up once fluoxetine was discontinued, and reappeared on re-exposure to fluoxetine. They also noted that a number of patients had a subsequent or prior response to monoamine oxidase inhibitors (MAOIs).

Criticisms of these cases referred to the complicated clinical profile of these tertiary referral centre patients, and to the use of fluoxetine in higher than normal clinical doses, as well as the role of concomitant medication. The possibility that concomitant sedative medication might have minimized the problem was not noted.

Other studies followed from authors noted for their expertise on akathisia [2–6]. These studies provided further evidence of dose-response, as well as challenge, dechallenge and rechallenge (CDR) relationships, the emergence of an agreed mechanism by which the effects were mediated and demonstrations that interventions could ameliorate the problems. A subsequent series of reports of suicidality and akathisia on sertraline and paroxetine pointed to the possibility of an SSRI-induced suicidality being a class effect [7]. Studies linking hospital admission to SSRI-linked manic or psychotic reactions indicate that akathisia (agitation) may not be the only mechanism whereby these drugs could produce a problem [8].

CDR and dose-response relationships have been the conventional means for establishing cause and effect relationships between drugs and adverse events as laid out by clinical trial methodologists [9–11], company investigators [12–14], medico-legal authorities [15] and the Courts [16]. Far less consistent evidence led British regulators to state unambiguously that benzodiazepines can trigger suicide [17]. Skeptics, however, have argued for additional RCT and epidemiological data.

Whether RCTs are needed to establish causality in this domain is an issue dealt with elsewhere [18], but specifically designed RCTs would have at least established the rates at which this seemingly new phenomenon might be happening, against the background of depression-related suicidality. Such studies would have provided a basis for estimating the public health impact of warnings or treatment monitoring.

Efficacy Studies

In lieu of specifically designed RCTs, therefore, the only available RCTs are those which formed the basis for the license application for recent antidepressants. An analysis was undertaken on this data by Khan et al. [19] to answer the question of whether it was ethical to continue using placebos in antidepressant trials; however, this analysis was not designed to determine whether SSRIs could trigger suicidality. While the FDA in general recommend that data from clinical trials be analysed both in terms of absolute numbers and patient exposure years (PEY), given that the object of this study was the hazard posed by placebo, the investigators appropriately analysed the figures in terms of PEY only. Khan et al. [19] found an excess of suicides and suicide attempts on antidepressants compared with placebo, which has been replicated in two other analyses of overlapping data sets [20, 21].

While an analysis in terms of exposure may be appropriate for an assessment of the risk posed by placebo, it is less inappropriate for a problem that clinical studies had linked to the first weeks of therapy. An analysis of suicidal acts on the basis of exposure will systematically select patients who do not have the problem under investigation, as those with the problem drop out of the trial, while others are kept on treatment for months on compassionate use grounds. Furthermore, an analysis in terms of exposure cannot readily deal with patients who are transferred from placebo to active drug or who are in dose-escalation protocols.

The data presented by Khan et al. [19] have accordingly been modified here in four respects. First, suicides and suicide attempts are presented in terms of the absolute numbers of patients. Second, based on an FDA paroxetine safety review [22] and FDA statistical reviews on sertraline [23], it is clear that some of the suicides and suicide attempts categorized in Khan et al. [19] as occurring on placebo actually occurred during a placebo wash-out peri-

The original clinical studies had suggested that there might be a very small vulnerable subpopulation of patients at risk from SSRIs, against a background of a much larger number of patients helped by the drugs. The original studies also focused on drug-induced suicidal ideation rather than actual suicides or suicide attempts. Focusing on suicidal acts gives a much less ambiguous outcome. Assuming a larger number of those exposed become suicidal rather than actually engage in a suicidal act, these RCT findings suggest that the at-risk group may in fact be larger than was initially thought.

Meta-Analyses of Suicidality on SSRIs

In addition to the data indicating an excess of suicidal acts on SSRIs in these RCTs, the clinical trials on zimelidine, the first SSRI, suggested there was a greater number of suicide attempts on it than on comparators. Montgomery et al. [27], however, demonstrated that while this might be the case, zimelidine appeared to do better than comparators in reducing already existing suicidal thoughts. A similar analysis demonstrated benefits for fluvoxamine against a backdrop of a suicide attempt rate that was higher than the comparator rate in clinical trials [28]. The problems with paroxetine noted above have led to similar analyses [29, 30].

The best-known analysis of this type was published by Lilly and indicated that 'data from these trials do not show that fluoxetine is associated with an increased risk of suicidal acts or emergence of substantial suicidal thoughts among depressed patients' [31]. Lilly's analysis has a number of methodological problems, however, which apply to a greater or lesser extent to all other such exercises. First, none of the studies included in the analysis were designed to test whether fluoxetine could be associated with the emergence of suicidality. Second, some of the fluoxetine studies used in this analysis had in fact been rejected by the FDA. Third, only 3,067 patients of the approximately 26,000 patients entered into clinical trials of fluoxetine were included in this meta-analysis. Fourth, no mention was made that benzodiazepines had been coprescribed in the clinical trial program in order to minimize the agitation that Lilly had recognized fluoxetine could cause [32]. Fifth, no reference was made to the 5% of patients who dropped out for anxiety and agitation. This drop-out rate, which is statistically significantly greater than for placebo, holds true for other SSRIs as well. Omitting these patients is surprising given that this was arguably the very problem that was at the heart of the issue, and DSM-IV-TR has since connected akathisia with suicide risk [33].

Sixth, this and other analyses depend critically on item-3 of the Hamilton Rating Scale for depression; this approach to the problem is methodologically unsatisfactory. The argument in these meta-analyses has broadly speaking been that in these randomized trials, the SSRI has reduced suicidality on item-3 of the Hamilton Rating Scale for depression and that there has not been an emergence of suicidality as measured by this item. To claim that the prevention of or reduction of suicidality in some patients in some way means that treatment cannot produce suicidality in others is a logical non sequitur. To argue that item-3 would pick up emergent suicidality in studies run by clinicians not aware of a possible adverse effect in this domain is a claim that has no evidence to support it. At the very least, item-3 would be much less sensitive than a specifically designed emergence of suicidality scale.

Despite these analytic quirks, the claim that SSRIs reduce suicidality in some patients appears strong. However, in so far as SSRIs reduce suicidality, and presumably suicidal acts in some, if there is a net increase in suicidal acts on SSRIs from these same trials, the extent to which SSRIs cause problems for some patients must be greater than is apparent from the RCT data outlined above.

Studies in Recurrent Brief Depression

There have been 3 studies in patients with recurrent brief depression, a patient group with high rates of suicide attempts, where suicide provocation would be difficult to demonstrate. In 1994, Montgomery et al. [34] reported that a study of fluoxetine carried out in recurrent brief depression indicated a lack of association between fluoxetine and suicide provocation. But the published paper contains figures on 107 of a target population of 150 patients, and of the 107, half dropped out, making it impossible, in the absence of convincing data on reasons for drop-out, to say that fluoxetine had no effect on the emergence of suicidal ideation. Claims that there is no linkage are hard to sustain against a background of an unpublished analysis of the results from the study which shows that placebo was significantly superior to fluoxetine ($p = 0.001$) [35].

These findings for fluoxetine are more consistent with data for suicide attempts on paroxetine in a trial for recurrent brief depression, in a study which had a projected

annual rate of suicide attempts in its paroxetine arm of 45 compared with 12 in the placebo arm, when it was terminated early [36].

A final study in this patient group also compared paroxetine and placebo [37]. This study reported that paroxetine reduced suicidal ideation and acts in some patients. However, 75% of both the paroxetine and placebo groups had dropped out by the end of the study, leaving only 19 out of a projected 100 patients for analysis. In the absence of details on drop-outs, it is impossible to decide whether paroxetine had precipitated suicidal ideation or attempts in some.

The randomization component of these studies along with that in the efficacy studies above controls for any suggestion that the results from the epidemiological studies outlined below stem from a preferential prescribing of SSRIs to suicidal patients.

Epidemiological Studies

Epidemiology traditionally involves the study of representative samples of the population and requires a specification of the methods used to make the sample representative. A series of what have been termed epidemiological studies has been held to exonerate SSRIs. The first is a one-column letter involving no suicides [38]. The second is a retrospective chart review [39], involving no suicides, which, analysed by others, shows a 3-fold increased relative risk of emergent suicidality for fluoxetine versus other antidepressants [40, 41].

A third was conducted on 654 anxious patients [42], of whom only 192 got fluoxetine and in which the only suicide occurred in a patient taking fluoxetine. A fourth study on 632 patients, instituted 10 years before fluoxetine had been launched, included only 182 patients who had got fluoxetine at any point [43]. None of these studies were clearly designed to establish whether fluoxetine might induce suicidality, and they lack a number of the methodological features standard for epidemiological studies.

Other studies have not exonerated SSRIs. Two of these, better described as post-marketing surveillance than epidemiological studies, comparing SSRI with non-SSRI antidepressants, found an increased rate of induction of suicidal ideation, although not suicide attempts or suicides, with SSRIs [44, 45].

In a population-based epidemiological study of 222 suicides, Donovan et al. [46] reported on 41 suicides who had had an antidepressant in the month before their suicide; this study demonstrated a statistically significant doubling of the relative risk of suicide on SSRIs compared with tricyclic antidepressants.

Table 2. Drug safety research unit studies of SSRIs and mirtazapine in primary care in the UK

Drug	Patients	Suicides	Suicides/ 100,000 patients
Fluoxetine	12,692	31	244 (CI 168–340)
Sertraline	12,734	22	173 (CI 110–255)
Paroxetine	13,741	37	269 (CI 192–365)
Fluvoxamine	10,983	20	183 (CI 114–274)
Total SSRIs	50,150	110	219/100,000
Mirtazapine	13,554	13	96 (CI 53–158)

In a further epidemiological study of 2,776 acts of deliberate self-harm, Donovan et al. [47] demonstrated a doubling of the risk for deliberate self-harm on SSRIs compared with other antidepressants, which was statistically significant for fluoxetine compared with commonly prescribed tricyclic antidepressants. The incidence of both suicides and suicide attempts in RCTs outlined above make it clear that this result is unlikely to stem solely from preferential prescribing to patients more at risk of suicidal acts.

A further set of post-marketing surveillance studies were carried out in primary care by the British Drug Safety Research Unit (DSRU) [48]. These studies recorded 110 suicides in over 50,000 patients being treated in primary care in Britain. The DSRU methodology has since been applied to mirtazapine, where there have been 13 suicides reported from a population of 13,554 patients [49], permitting the comparisons outlined in table 2.

A further study from British primary care was undertaken by Jick et al. [50], which investigated the link between antidepressant prescriptions in 143 suicides from over 200,000 patient exposures. It produced a statistically significant doubling of the relative risk of suicide on fluoxetine compared with the reference antidepressant, dothiepin, when calculated in terms of PEY. Controlling for confounding factors such as age, sex and previous suicide attempts left the relative risk at 2.1 times greater for fluoxetine compared with dothiepin and greater than for any other antidepressant studied, although statistical significance was lost in the process. To provide comparability with other figures, I have recalculated this data in terms of absolute numbers (table 3).

Table 3. Suicides on antidepressants in primary care in the United Kingdom [50]

Drug	Suicide rate/ 100,000 patients	Absolute suicide numbers
Dothiepin	70 (CI 53–91)	52/74,340 pts.
Lofepramine	26 (CI 8–61)	4/15,177 pts.
Amitriptyline	60 (CI 41–84)	29/48,580 pts.
Clomipramine	80 (CI 37–138) (38–144)	9/11,239 pts.
Imipramine	47 (CI 24–107) (20–90)	7/15,009 pts.
Doxepin	69 (CI 18–190) (17–180)	3/4,329 pts.
Flupenthixol	78 (CI 43–129)	13/16,599 pts.
Trazodone	99 (CI 31–230)	4/4,049 pts.
Mianserin	166 (CI 86–285)	11/6,609 pts.
Fluoxetine	93	11/11,860 pts.
Total excluding fluoxetine		132/195,931 pts. 67/100,000 pts.

pts. = Patients.

The figures from the studies by Jick et al. [50] and DSRU allow comparisons between antidepressants, but shed no light on the comparison between treatment with antidepressants and non-treatment or on the efficacy of antidepressants in reducing suicide risk in primary care. The traditional figures with which the DSRU studies and the study by Jick et al. [50] might be compared are a 15% lifetime risk for suicide for affective disorders, a figure of 15,000/100,000 patients or approximately 300/100,000 patient-years. Against this, the Jick figure of 189/100,000 patient-years for fluoxetine does not seem excessive.

A 15% figure, however, was derived from hospitalized samples of melancholic depressives in the pre-antidepressant era. There are very few empirical figures available for suicide rates in primary care depression, the sample from which the Jick and DSRU figures come. One set of figures stems from Sweden [51], which gives a figure of 0 per 100,000 patients, for the suicide rate in non-hospitalized depression. Another primary care figure from Holland gives a suicide rate of 33 per 100,000 patient-years [52]. Finally, Simon and VonKorff [53] from Puget Sound, based on a study of 65,000 patient-years and 36 suicides, give figures for patients with any secondary mental health service contact as 64/100,000 patient-years. Primary care depression treated with antidepressants had a suicide rate of 43/100,000 patient-years, while primary care depressions not treated with antidepressants had a suicide rate of 0/100,000 patients, although the possibility that antidepressant prescribing may have been associated with greater severity must not be discounted.

Utilizing a database of 2.5 million person-years and 212 suicides from North Staffordshire, Boardman and Healy [54] have modelled the rate for suicide in treated or untreated UK depressives and found it to be of the order of 68/100,000 patients for all affective disorders. The figure of 68/100,000 gives an upper limit on the figure of suicides in mood disorders compatible with observed national suicide rates in the United Kingdom. The study by Boardman and Healy [54] gives a figure of 27/100,000 patients per annum for primary care primary affective disorders. It is not possible to compare these figures with those derived from the DSRU study or the study by Jick et al. [50] with confidence, but a rough calculation suggests a relative risk of suicide of 3.0 or greater for treatment with SSRI antidepressants in this population versus treatment with non-SSRI antidepressants or non-treatment.

There are two additional points of note. First, the low rates of suicides in untreated primary care mood disorder populations stemming from these epidemiological figures are consistent with the low rate of suicides on placebo in the antidepressant RCTs outlined above. Second, correcting the DSRU figures for exposure lengths gives figures for suicides on sertraline and paroxetine compatible with those reported from RCTs calculated in terms of exposure lengths by Khan et al. [19].

National Suicide Rates

There is a further broadly epidemiological argument put forward by Isacsson [55]. It argues that there is evidence that increased use of antidepressants, primarily SSRIs, has been associated with a lowering of national suicide rates. There is some evidence for this from Sweden but contrary evidence from Italy [56] and from Ireland, where rising national suicide rates have been positively linked by epidemiology to SSRI use [57]. Despite a certain implausibility to the idea that antidepressant treatment could lower national suicide rates [58], the argument by Isacsson [55] has been extrapolated to US figures based on figures for overall suicide rates in recent years. US suicide rates, however, can support almost any argument. Showing figures from the overall age-adjusted rate from 1979 to 1997 indicates a drop from 11.6 to 10.6 per 100,000 people. Seventy-five percent of Americans committing suicide, however, are white males. Looking at these figures through the entire time period for which age-adjusted

rates are available shows figures of 18.5 in 1979 versus 18.4 in 1997, suggesting that any change in the overall rate might be as likely to stem from changes in the ethnic mix of the population rather than for any other reason.

Healthy Volunteer Studies

The debate on SSRIs and suicidality has centred on the relative contributions stemming from the disease, depression, and from the treatment. Healthy volunteer studies have the power to contribute to this issue by removing depression from the equation. In a recent study, giving 4–8 mg of reboxetine or a dose of 50–100 mg of sertraline, in a double-blind randomized crossover design to 20 medical, nursing and administrative colleagues, Tranter et al. [59] found that two volunteers became intensely suicidal [60]. Attempting to put ORs or to otherwise handle such data is difficult, but one estimate of the chances of two perfectly normal people becoming actively suicidal in the course of any 2-week period during the year has been put at approximately 1 in 2,000 [61]. The figure of 2 in 20 being suicidal is consistent with a patient drop-out rate of 1 in 20 for agitation in SSRI clinical trials.

Few of the healthy volunteer studies done by SSRI companies as part of their development work have been published. In the case of fluoxetine, 12 out of 53 healthy volunteer studies have been reported. From 35 healthy volunteer pre-launch paroxetine studies approximately 14 have appeared. As few as 7 of approximately 35 pre-launch sertraline studies have been published, with unpublished studies including 1 in which all volunteers dropped out apparently for agitation. In the case of published work, the data reported commonly exclude material concerning behavioural toxicity, including the suicide of at least 1 volunteer.

Among the published studies with sertraline, 1 demonstrates a clear dose-dependent induction of agitation with sertraline [62]. Warrington et al. [63] in a study of paroxetine reporting a 15% drop-out rate on paroxetine among healthy volunteers, with none on amitriptyline, concluded that 'antidepressants are poorly tolerated in healthy volunteers'.

These healthy volunteer studies have a further significance for risk-benefit assessments. The possibility that antidepressants might induce suicidality was recognized in the first trial of imipramine [64]. This hazard was once rationalized by an acceptance that antidepressants were being given to individuals who were at risk and that any hazard the drugs posed would be offset by the reduction in overall hazard. In the course of the 1990s, however, as we have detected cases of depression in primary care settings, these findings from healthy volunteer studies, as well as those from the recent RCTs outlined above, which have largely been conducted in primary care settings, indicate that traditional risk-benefit assessments may need to be rethought.

Paradoxically, healthy volunteer studies may offer a way forward. In addition to finding an unexpected induction of suicidality on sertraline, studies of healthy volunteers have found an interaction between personality type and response to antidepressants differentially selective to brain monoamine systems [59]. There may be patients suited to selective agents, in whom indicators of efficacy are likely to be much greater than are found in an unselected sample of patients and for whom the risk benefit ratio as regards suicidality is likely to be more favourable. Other patients may be correspondingly less suited to a particular selective agent. Healthy volunteer studies have the potential to help determine what constitutional or other pharmacogenetic factors may be involved here.

Future Directions

Where early clinical studies had pointed to SSRI-induced suicidality using conventional cause and effect criteria, subsequent randomized trials appear to confirm the existence of a risk. The magnitude of this risk is difficult to determine given that antidepressants may both increase that risk for some and minimize it for others, but RCTs reviewed here point to at least a doubling of relative risk. Epidemiological and healthy volunteer studies appear to confirm this risk.

However, the RCTs reported here were undertaken before antidepressant-induced suicidality had become an issue. The studies in the public domain give indications of the population size that might be appropriate to shed further light on some of the issues, utilizing already existing databases. Each of the main SSRI companies now has studies, which contain tens of thousands of patients with hundreds of suicides and suicide attempts per drug. Making a full set of studies for both depression and non-depression indications available would move the debate on.

While a fuller set of data from already completed studies would move the issues forward, assessments of the magnitude of any risk that treatments pose and the characteristics of any patients who may be at risk should ideally be based on studies specifically designed to shed light

on these issues. The simple addition of a rating scale sensitive to the emergence of suicidal ideation to current RCT protocols would yield significant information without raising ethical concerns.

Hitherto, there has been a legitimate public health argument for wondering whether raising concerns about hazards might deter people at risk for suicide from seeking treatment, possibly leading thereby to an increased population risk of suicide. The data reviewed here suggest that warnings and monitoring are more likely to reduce overall risks or that at least we should adopt a position of clinical equipoise on this issue and resolve it by means of further data rather than on the basis of speculation.

Competing Interests David Healy

In recent years, I have had consultancies with, have been a principal investigator or clinical trialist for, a chairman or speaker at international symposia for or in receipt of support to attend meetings from:

Astra, Astra-Zeneca, Boots/Knoll Pharmaceuticals, Eli Lilly, Janssen-Cilag, Lorex-Synthelabo, Lundbeck, Organon, Pharmacia & Upjohn, Pierre-Fabre, Pfizer, Rhone-Poulenc Rorer, Roche, SmithKline Beecham, Solvay, Zeneca.

I have been expert witness for the plaintiff in five legal actions involving SSRIs and have been consulted on a number of other attempted suicide, suicide and suicide-homicide cases following antidepressant medication, in the majority of which I have offered the view that the treatment was not involved. I have also been an expert witness for the defence on a series of LSD (46) and ECT (1) cases.

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