ANTIDEPRESSANTS & SUICIDE:
RISK-BENEFIT CONUNDRUMS

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Abstract

Background: There has been a long-standing controversy about the possibility that SSRI antidepressants might induce suicidality in some patients.

Methods: This paper reviews available RCTs, the meta-analyses undertaken of clinical trials to investigate the issues further and epidemiological studies to shed light on this issue.

Results: The original clinical studies raising concerns about SSRIs and suicide induction 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 suicidal acts on active treatments compared to placebos with an Odds Ratio of 2.4 (95% Confidence Interval is 1.6 – 3.7). This excess of suicidal acts also appears in epidemiological studies.

Conclusions: The data reviewed make it difficult to sustain a null hypothesis 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

The debate regarding SSRIs and suicide started in 1990, when Teicher, Glod and Cole described six cases in which intense suicidal preoccupation emerged during fluoxetine treatment (1). This paper was followed by others (2,3,4,5,6), which combined provided evidence of dose response, challenge, dechallenge and rechallenge relationships as well as the emergence of an agreed mechanism by which the effects were mediated and demonstrations that interventions in the process could ameliorate the problems. A subsequent series of reports of suicidality and akathisia on sertraline and paroxetine pointed to SSRI-induced suicidality being a class effect rather than something confined to fluoxetine (7).

An induction of suicidality on SSRIs, therefore, had apparently been convincingly demonstrated according to conventional criteria for establishing cause and effect relationships between drugs and adverse events as laid out by clinical trial methodologists, company investigators, medico-legal authorities and the Federal Courts (8). Far less consistent evidence led the Medicine's Control Agency in Britain in 1988 to state unambiguously that benzodiazepines can trigger suicide.

Specifically designed RCTs at this point would have established the rates at which this seemingly new phenomenon might be happening, against the background of depression related suicidality. However no studies designed to investigate these issues have ever been undertaken. This review, therefore, will in lieu cover the evidence for frequency of suicidal acts from RCTs of recently released antidepressants, the meta-analyses of efficacy studies in depression that have been brought to bear on the question, and relevant epidemiological studies.

Efficacy Studies

In lieu of specifically designed RCTs, therefore, one source of data are the RCTs, which formed the basis for the license application for recent antidepressants. An analysis was undertaken on this data recently by Khan et al to answer the question whether it was ethical to continue using placebos in antidepressant trials (9). While, the FDA in general recommend that data from clinical trials be analyzed both in terms of absolute numbers and patient exposure years (PEY), given that an assessment of the hazards posed by

placebo was the object of this study, the investigators appropriately analyzed the figures in terms of PEY only. Khan et al found an excess of suicidal acts on antidepressants compared to placebo, which has been replicated in two other analyses (10,11).

However, while an analysis in terms of patient exposure years may be appropriate for an assessment of the risk of exposure to placebo, it is inappropriate for the assessment of a problem that the clinical studies outlined above had clearly linked to the first weeks of active therapy. An analysis of suicidal acts on the basis of duration of exposure, will systematically select patients who do not have the problem under investigation, as those with the problem dropout of the trial, while others who do well are kept on treatment for months or more on compassionate use grounds.

The data presented by Khan and colleagues has accordingly been modified here in four respects. First, suicides and suicidal acts are presented in terms of the absolute numbers of patients. Second, based on an FDA paroxetine safety (12) and FDA statistical reviews on sertraline (13), it is clear that some of the suicides and suicidal acts categorized in Khan et al as occurring on placebo actually occurred during a placebo washout period. Placebo and washout suicides are distinguished here. Third based on a further article by Khan et al (14), data for citalopram is included (although no details about the validity of assignments to placebo are available). Fourth based on public domain documents, data for fluoxetine are presented, again breaking the figures into placebo and washout suicidal acts, along with data for venlafaxine (15).

-- See Table 1 --

When washout and placebo data are separated and analysed in terms of suicidal acts per patient, (excluding the figures for buproprion on the basis of missing data), using a Mantel-Haenszel procedure, the odds ratio of a suicidal act on these new antidepressants as a group compared to placebo is 2.4 (95% Confidence Interval is 1.6 – 3.7). The odds ratio for completed suicides on these antidepressants compared to placebo is 4.3 (95% Confidence Interval 1.1 – 17.8). The odds ratio for a suicidal act on SSRI antidepressants (including venlafaxine) compared to placebo is 2.2 (95% Confidence Interval 1.4 - 3.5), with an odds ratio for completed suicides on SSRIs compared to placebo of 2.4 (95% Confidence Interval 0.6 – 10.2). Chi-squared testing of

paroxetine compared to placebo yields an increase in suicidal acts compared to placebo ($p = 0.044$).

If washout suicidal acts are included with placebo, as the companies appear to have done, but adjusting the denominator appropriately, the relative risk of suicidal acts on sertraline, paroxetine or fluoxetine compared to placebo becomes significant with figures ranging from 3.0 for sertraline to over 10.0 for fluoxetine.

Other datasets yield similar findings. For instance in Pierre Fabre's clinical trial database of approximately 8,000 patients, the rate for suicidal acts on SSRIs appears to be 3 times the rate for other antidepressants (16). However these other datasets have a mixture of trials. The current analysis limits the number of studies but ensures that they should be roughly comparable and the selection of studies is based on regulatory requirements rather than individual bias.

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 were a greater number of suicide attempts on it than on comparators. Montgomery, however, demonstrated that while this might be the case, zimelidine appeared to do better than comparators in reducing already existing suicidal thoughts (17). 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 (18). Problems with paroxetine led to similar analyses and similar claims (19,20).

The best-known analysis of this type was published by Lilly after the controversy with fluoxetine emerged; it 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" (21). 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. In the case of fluoxetine, all of the studies had been conducted before concerns with suicide induction had arisen. Some of the fluoxetine studies used in their analysis by Lilly had in fact been

rejected by the FDA. Second, only 3,067 patients of the approximately 26,000 patients entered into clinical trials of fluoxetine were included in this meta-analysis. Third, no mention was made of the fact that benzodiazepines had been co-prescribed in the clinical trial program in order to minimize the agitation that Lilly recognized fluoxetine could cause (8). Fourth, no reference was made to the 5% of patients who dropped out for anxiety and agitation. Given that this was arguably the very problem that was at the heart of the issue, the handling of this issue was not reassuring. The 5% dropout rate for agitation/akathisia holds true for other SSRIs and the differences between SSRI and placebo are statistically significant. As DSM-IVTR has connected akathisia with suicide risk, this point is of importance (22).

Fifth, this and other analyses depend critically on Item 3 of the Hamilton Rating Scale for depression; this approach to the problem is one that FDA officials, Lilly personnel and Lilly's consultants (8) made it clear was 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 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 this possible adverse effect is a claim that has no evidence to support it.

Despite these methodological caveats, the claim that SSRIs reduce suicidality in some patients appears strong. However, in so far as SSRIs reduce 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 considering the raw data.

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 have been appealed to in this debate. The first is a one-column letter involving no suicides (23). The second is a selective retrospective post-marketing chart review (24), involving no suicides, which

analyzed by the ACNP, the FDA and others show a 3-fold increased relative risk of emergent suicidality for fluoxetine versus other antidepressants (25,26).

A third was conducted by Warshaw and Keller on anxious patients (27), in which the only suicide occurred in a patient taking fluoxetine. Of the 654 patients in this study only 192 got fluoxetine. This, therefore, was not a study designed to test fluoxetine's capacity to induce suicidality. A fourth study on 632 patients, conceived 20 years before fluoxetine was launched and instituted 10 years before launch, had only 182 patients who had got fluoxetine at any point (28). This was clearly not a study designed to establish whether fluoxetine might induce suicidality. Under the definition of epidemiology offered above, none of these studies qualify as epidemiology.

Although not properly epidemiological, two sets of post-marketing surveillance studies that have compared SSRI with non-SSRI antidepressants found a differential in the rate of induction of suicidal ideation, although not suicidal acts or suicides, with SSRIs compared to non-SSRIs (29,30).

In a more standard epidemiological study of 222 suicides, Donovan et al reported on 41 suicides that 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 to tricyclic antidepressants (31).

In a further epidemiological study of 2,776 acts of deliberate self-harm, Donovan et al (32) demonstrated a doubling of the risk for deliberate self-harm on SSRIs compared with other antidepressants.

A further set of post-marketing surveillance studies were carried out in primary care in the United Kingdom by the Drug Safety Research Unit (DSRU) (33). These studies recorded 120 suicides in over 44,000 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 (34). This permits the comparisons outlined in Table 2.

-- See Table 2 --

A further study from British primary care was undertaken by Jick and colleagues (35). This investigated the link between antidepressant prescriptions in 143 suicides from over 200,000 patients. 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 patient exposure years. Controlling for confounding factors such as age, sex and previous suicide attempts, left the relative risk at 2.1 times greater for fluoxetine compared to dothiepin and greater than for any other antidepressant studied, although statistical significance was lost in the process. Of further note are the elevated figures for mianserin and trazodone, which are closely related pharmacologically to mirtazapine and nefazodone. Controlling for confounding factors in the case of mianserin and trazodone, however, led to a reduction in the relative risk of these agents compared to dothiepin.

To provide comparability with other figures, I have recalculated this data in terms of absolute numbers and have separated the figures for fluoxetine from other figures (Table 3).

-- See Table 3 --

The figures in the Jick study however only allow comparisons between antidepressants. They 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 Jick study might be compared are a 15% lifetime risk for suicide for affective disorders. This would be inappropriate, however, as this 15% figure 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 (36), which gives a suicide rate of zero per 100,000 patients in non-hospitalized depression. Another primary care figure from Holland gives a suicide rate of 33 per 100,000 patient years (37). Finally Simon and VonKorff 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 (38). 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.

Utilizing a database of 2.5 million person years and 212 suicides from North Staffordshire, Boardman and Healy have modeled the rate for suicide in treated or untreated UK depressives and find it to be of the order of 68/100,000 patient years for all affective disorders (39). The figure of 68/100,000 gives an upper limit on the figure of suicides in mood disorders that are compatible with observed national rates of suicide in the United Kingdom. The Boardman and Healy study gives a figure of 27/100,000 patients per annum for primary care primary affective disorders. Possible relative risks for SSRIs from the DSRU studies set against these figures and the findings from the Jick study for all antidepressants excluding fluoxetine are presented in Table 4.

-- See Table 4 --

Comparing the figures for SSRIs from Table 2 with those for the non-SSRI antidepressants from the Jick Study gives a mean figure for non-SSRI antidepressants of 68 suicides per 100,000 patients exposed compared with a figure of 212 suicides for the SSRI group. Based on an analysis of 249,803 exposures to antidepressants, therefore, the broad relative risk on SSRI antidepressants compared to non-SSRI antidepressants or even non-treatment is 234/68 = 3.44.

There are two points of note. First, these low rates for suicide in untreated primary care mood disorder populations are consistent with the rate of zero suicides on placebo in antidepressant RCTs. Second, correcting the DSRU figures for exposure lengths gives figures for suicides on sertraline and paroxetine compatible with those reported from RCTS by Khan et al (9).

Concluding Remarks

Since antidepressant drug treatments were introduced, there have been concerns that their use may lead to suicide (40). Hitherto, there has been a legitimate public health argument for wondering whether raising concerns about hazards might deter people at risk from suicide from seeking treatment, possibly leading to an increased number of

suicides. The data reviewed here, however, 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.

The evidence that antidepressants may reduce suicide risk is strong from both clinical practice and RCTs. An optimal suicide reduction strategy would probably involve the monitored treatment of all patients, and some restriction of treatment to those most at risk of suicide. In addition, given evidence that particular personality types suit particular selective agents and that mismatching patients and treatments can cause problems (41), further exploration of this area would seem called for.

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Table 1: Incidence of Suicides and Suicide Attempts in Antidepressant Trials From Khan et al (2000 & 2001), & Von Keitz 1986 (Refs 9, 14, 15)

Investigational Drug	Patient No	Suicide No	Suicide Attempt No	Suicides & Attempts as a % of Patient No
Sertraline hydrochloride	2,053	2	7	0.44%
Active comparator	595	0	1	0.17%
Placebo	786	0	2	0.25%
Placebo Washout		0	3	
Paroxetine hydrochloride	2,963	5	40	1.52%
Active comparator	1151	3	12	1.30%
Placebo	554	0	3	0.54%
Placebo Washout		2	2	
Nefazodone hydrochloride	3,496	9	12	0.60%
Active comparator	958	0	6	0.63%
Placebo	875	0	1	0.11%
Mirtazapine	2,425	8	29	1.53%
Active comparator	977	2	5	0.72%
Placebo	494	0	3	0.61%
Bupropion hydrochloride	1,942	3	----	
Placebo	370	0	----	
Citalopram	4,168	8	91	2.38%
Placebo	691	1	10	1.59%
Fluoxetine	1,427	1	12	0.91%
Placebo	370	0	0	0.00%
Placebo Washout		1	0	
Venlafaxine	3082	7	36	1.40%
Placebo	739	1	2	0.41%
All Investigational drugs	21,556	43	232	1.28%
All SSRIs	13,693	23	186	1.53%
Active comparator	3,681	5	24	0.79%
Total Placebo	4,879	2	21	0.47%
SSRI Trial Placebo	3,140	2	16	0.57%

Table 2:

Drug Safety Research Unit Studies of Selective Serotonin Reuptake Inhibitors & Mirtazapine in Primary Care in the United Kingdom.

Drug	**No. Patients**	**No. Suicides**	**Suicides/ 100,000 Patients**
Fluoxetine	12692	31	244 (C.I. 168 – 340)
Sertraline	12734	22	173 (C.I. 110 – 255)
Paroxetine	13741	37	269 (C.I. 192 – 365)
Fluvoxamine	10983	20	183 (C.I. 114 – 274)
Total SSRIs	**50150**	**110**	**219/100,000**
Mirtazapine	13,554	13	96 (C.I. 53 – 158)

Table 3:

Suicides on Antidepressants in Primary Care in the United Kingdom:

From Jick et al (1995).

Drug	**Suicide Rate/ 100,000 Patients**	**Absolute Suicide Numbers**
Dothiepin	70 (C.I. 53 – 91)	52 Suicides in 74,340 Pts
Lofepramine	26 (C.I. 8 – 61)	4 Suicides in 15,177 Pts
Amitriptyline	60 (C.I. 41 – 84)	29 Suicides in 48,580 Pts
Clomipramine	80 (C.I. 38 – 144)	9 Suicides in 11,239 Pts
Imipramine	47 (C.I. 20 – 90)	7 Suicides in 15,009 Pts
Doxepin	69 (C.I 17 – 180)	3 Suicides in 4,329 Pts
Flupenthixol	78 (C.I. 43 – 129)	13 Suicides in 16,599 Pts
Trazodone	99 (C.I. 31 – 230)	4 Suicides in 4,049 Pts
Mianserin	166 (C.I. 86 – 285)	11 Suicides in 6,609 Pts
Fluoxetine	93	11 Suicides in 11,860 Pts
Total excluding Fluoxetine		**132 Suicides per 195,931 Patients** **67 Suicides per 100,000 Patients**

Table 4:

The Relative Risk of Suicide on SSRIs from DSRU Studies Compared to the General Risk of Suicide in UK Primary Care Primary Affective Disorders (Boardman & Healy) & in UK Primary Care Depression Treated with Non-SSRI Antidepressants (Jick).

	Compared to Primary Care Primary Affective Disorders (Boardman, Healy 2001)	**Compared to Primary Care Depression Treated with non-SSRI Antidepressants (Jick et al 1995)**
Sertraline	6.4	2.54
Fluoxetine	9.2	3.59
Paroxetine	10.2	3.96
Total SSRI	**8.3**	**3.44**