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Antidepressant drug use & the risk of suicide

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Summary
There have been longstanding concerns about the propensity of antidepressants to precipitate suicidality in vulnerable individuals. To investigate this further, first we have analyzed all clinical trials, and in particular trials submitted to regulators for evidence on the relative risk of antidepressants versus placebo for this hazard. Second, we have compiled current epidemiological evidence germane to the issue. Third, we have constructed a model (Investigative Medication Routine; IMR) to shed light on the interactions between drug uptake, patient numbers on treatment and suicidal events. The clinical trial data gives rise to a relative risk of suicide on antidepressants over placebo of the order of a 2.0–2.5 times greater risk with treatment. These figures are supported by epidemiological findings. Investigative Medication Routine translates such findings into estimates of likely adverse outcomes, and explains why apparently increasing consumption of antidepressants would not be expected to lead to increased national suicide rates. From this data, we conclude that there is a clear signal that suicides and suicidal acts may be linked to antidepressant usage. It would seem likely that explicit warnings and monitoring in the early stages of treatment could greatly minimize these hazards.

Introduction

The notion that antidepressants might precipitate suicide in depressed patients was first raised in 1958 (Kielholz & Battegay, 1958). Part of the risk was linked to a phenomenon recently termed the rollback phenomenon, which refers to a risk that antidepressants might mobilise severely depressed and still suicidal patients, making a suicide attempt more likely. But part of the risk was also linked to a more direct drug induced provocation of problems, as Kielholz's later formulations of these issues recognized that more activating antidepressants (*viz* monoamine oxidase inhibitors; MAOIs) were more likely to cause problems than sedating antidepressants (Kielholz, 1971).

For 30 years antidepressants were primarily used in severely depressed and often hospitalized patients. These patients were at high risk of suicide and therefore even if treatment posed a risk, successful treatment had a favourable risk benefit ratio. Furthermore these patients were usually supervised early in treatment so that developing problems could be recognized and managed. For the past 15 years however the majority of patients treated with 'antidepressants' have been treated unsupervised in primary care and increasingly have had less severe depressive disorders or one of a number of anxiety disorders. Against this background the potential risks that antidepressants pose have become more salient.

The question of suicidality on selective serotonin reuptake inhibitors (SSRIs) achieved public prominence with reports from Teicher, Glod & Cole (1990) that Prozac could trigger suicidality in patients. Fourteen years later, warnings were put on antidepressants indicating there may be difficulties during the early phase of treatment, during treatment discontinuation, and when the dose of treatment is being changed, and that treatment related risks may be present in patients being treated for syndromes other than depression, such as anxiety or smoking cessation.

In traditional assessments of causality, challenge, de-challenge and re-challenge (CDR) and dose response relationships between an agent and an adverse outcome are the recognized methods of establishing causality. In the case of the SSRIs, CDR and dose response relationships between treatment and suicidality in depressed patients have been present for some time (Healy & Whitaker, 2003). The appearance of the problem in populations not at risk for that problem is further evidence for a causal link, such as patients with obsessive-compulsive disorder, or stress-induced urinary incontinence or healthy volunteers.

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The frequency of problems: Evidence from trials

The availability of CDR, and dose response evidence gives no indication as to the frequency at which problems may be happening. Potential estimates of frequency can be derived from clinical trials.

Fergusson et al. (2005) have searched all published SSRI trials for evidence on suicides and suicidal acts. These trials have a number of limitations. First, the trials were not designed to detect suicidality. Second, agitation and anxiety occurring in these trials were commonly treated with benzodiazepines, or with other agents, or by dropout. Third, dropouts were often lost to follow-up, so that the true rate of suicidal acts remains unknown. Fourth, there is evidence of under-reporting of serious adverse events; based on known suicidal acts from the Food and Drug Administration (FDA) reviews, a best estimate is that no more than one in four suicidal acts in antidepressant trials are reported in the scientific literature. Fifth, a large proportion of the trials had dropout rates in excess of 30%, and sample sizes no greater than 50 patients. Sixth, many trials with particularly adverse outcomes, including any specifically designed to investigate the occurrence of suicidality remain unpublished or misleadingly published (*viz* Montgomery et al., 1994; Montgomery, 1997).

Nevertheless, the combined literature points to an excess of suicidal acts on SSRIs compared to placebo from as early as 1988, even though many early trials failed to report on suicidal acts. In total, of 3,717 citations, 677 trials met inclusion criteria, involving 85,470 patients, and these gave rise to a 2.28 relative risk of suicide attempts (95% confidence interval [CI]: 1.14–4.55) for patients receiving SSRIs compared to placebo.

A less selected dataset is the set of antidepressant trials lodged with the FDA and other regulators for registration purposes. Two analyses of this database have taken place. One set of analyses, undertaken by Khan, Khan, Kolts and Brown (2003), Khan, Warner and Brown (2000), and Storosum, van Zwieten, van den Brink, Gersons and Broekman (2001), points to an excess of suicidal acts on SSRIs and other antidepressants compared to placebo, with a relative risk of the order of 1.5 (95% CI: 0.6–3.6) (Khan et al., 2003).

There are two points to note about these figures. First, in this context a relative risk of 1.5 is a relative risk for the balance of benefits and hazards on treatment rather than for the occurrence of hazards; if it is thought there is a beneficial effect of treatment on suicide and suicidal act rates, then the relative risk of treatment induced hazards minus treatment induced benefit must necessarily be greater than 1.5.

Second, one interpretation of a 95% confidence interval for suicides and suicidal acts between active treatment and placebo that overlaps 1.0 is that there is no difference between active medication and placebo. This interpretation might be appropriate in an analysis of a hypothesis testing study, with a sufficiently powered sample size. But these trials were not in fact designed to or powered to test for differences in suicidal act rates, in which case the correct interpretation for the results from Kahn et al. (2003) and Storosum et al., (2001) is that the best estimate for the balance of risks and benefits is 1.5 and that the scientific data is consistent with a hazard that may be occurring up 3.6 times more frequently on active treatment.

Several analyses have been conducted of individual drugs within this group of antidepressants. Thus Montgomery, Dunner & Dunbar (1995) claimed that trial data indicated a five-fold lowering of risk of suicidal acts in patients taking paroxetine compared to placebo, when duration of exposure is taken into account. This approach is standard across analyses for fluoxetine and other antidepressants, but is methodologically incorrect, as it breaches randomization by selecting patients with favourable responses to treatment and weights the results by including the greatly extended exposures of such subjects to treatment.

A further set of analyses, undertaken by Healy and Whittaker (2003), incorporate a more detailed scrutiny of the FDA medical reviews of these drugs than undertaken by Khan et al. (2000, 2003) and do not analyze by duration of exposure. This review of the FDA records has revealed that a number of suicides and suicidal acts that have occurred during the washout and follow-on phase of clinical trials, as well as events from the post-completion phase of trials, have, in the case of fluoxetine, sertraline and paroxetine, been inappropriately included in the placebo group (see Figures 1 and 2).

When washout and placebo data are separated and analyzed in terms of suicidal acts per patient (see Table I), (excluding the figures for buproprion on the basis of missing data), using an exact Mantel–Haenszel exact conditional test for independence, with a one-tailed test for significance, the odds ratio of a suicide on new antidepressants as a group compared to placebo is 4.40 (95% CI: 1.32–infinity; $p = 0.0125$). The odds ratio for a suicidal act on these antidepressants compared to placebo is 2.39 (95% CI: 1.655–infinity; $p < 0.0001$). The odds ratio for a completed suicide on an SSRI antidepressant (including venlafaxine) compared to placebo is 2.46 (95% CI: 0.707–infinity; $p = 0.16$), with an odds ratio for a suicidal act on SSRIs compared to placebo of 2.22 (95% CI: 1.47–infinity; $p < 0.001$).

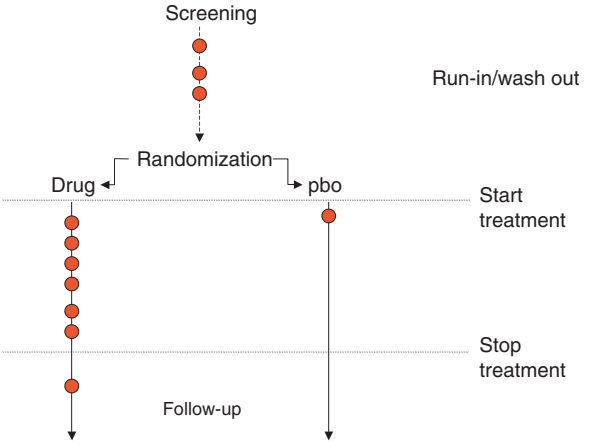

Figure 1. Fluoxetine-paroxetine-sertraline adult trials: Occurrence of suicidal acts.

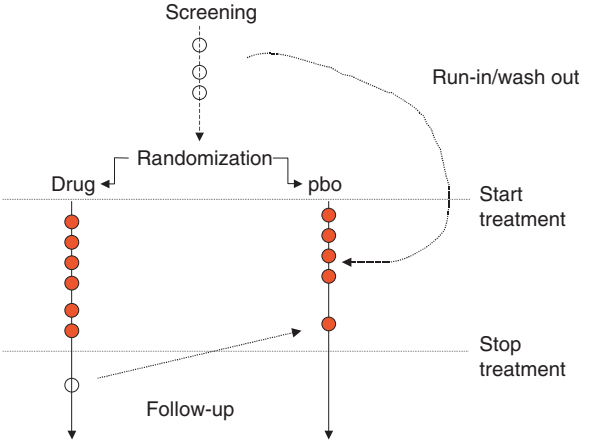

Figure 2. Fluoxetine-paroxetine-sertraline adult trials: Analysis of suicidal acts. Suicides and suicidal acts in SSRI clinical trials are schematically represented as red dots here. The published literature inappropriately follows Figure 2 rather than Figure 1.

A further analysis of clinical trial data from adults by FDA officers (Hammad, Mosholder, Boehm, Racoosin & Laughren, 2003) found the following relative risks of suicide: atypical antidepressants compared to placebo is 2.66 (95% CI: 2.40, 2.95); on SSRIs compared to placebo is 1.50 (95% CI: 1.35, 1.66); tricyclic antidepressants compared to placebo is 2.10 (95% CI: 1.84, 2.39), and for all antidepressants compared to placebo is 1.98 (95% CI: 1.81, 2.18). These authors do not report risk rates for suicidal acts. They also indicate that controlling for a variety of factors may minimize these risks, but controlling for selected factors *post-hoc* would appear to defeat the purposes of randomization.

Finally, in the course of 2004 there have been a series of analyses of suicidal events from clinical trials of antidepressants in paediatric populations. These have yielded a variety of risk estimates based on determinations of which events are counted as suicidal. At an FDA hearing (2nd February 2004) the relative risk offered was 1.7 (95% CI: 1.2, 2.4; $p < 0.0014$) (Laughren, 2004). All estimates concur on the existence of a risk and the fact that this risk is present in both depressed and non-depressed populations. An FDA hearing (14th September 2004) adjudged the link between antidepressant usage and suicidal events to be causally related.

The frequency of problems: Evidence from pharmacoepidemiology

The data from randomized controlled trials (RCTs) needs supplementing with studies from naturalistic settings. The Drug Safety Research Unit (DSRU) in Southampton has conducted a series of post-marketing studies on each of the SSRIs following their launch (MacKay et al., 1997). These have recruited over 50,000 patients to treatment with fluoxetine, paroxetine, sertraline, and fluvoxamine, and yield a mean estimate of 212 suicides per 100,000 patients treated (see Table II).

These DSRU patients were subjects being treated in primary care, who were presumably at the normal

Table I. Incidence of suicides and suicide attempts in antidepressant trials (Healy & Whitaker, 2003).

Investigational drug	Patient no.	Suicide no.	Suicide attempt no.	Suicides & attempts as a % of patients
Sertraline	2,053	2	7	0.44%
Active comparator	595	0	1	0.17%
Placebo	786	0	2	0.25%
Placebo washout		0	3	
Paroxetine	2,963	5	40	1.52%
Active comparator	1151	3	12	1.30%
Placebo	554	0	3	0.54%
Placebo washout		2	2	
Nefazodone	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	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%

A report to FDA by Pfizer Inc., 14th September 1990 suggests the best figure for suicides and suicidal acts in the conventional phase of sertraline trials was two suicides and six suicidal acts in 2,053 patients on sertraline, and one suicidal act in 786 patients on placebo.

Table II. Drug Safety Research Unit studies of selective serotonin reuptake inhibitors in primary care in the UK.

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

primary care depression risk of suicide. This latter risk is unknown. There are very few empirical figures available for suicide rates in primary care depression. One study from Sweden (Hagnell, Lanke & Rorsman, 1981), by inference, 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 (Weel-Baumgarten, van den Bosch, van den Hoogen & van Zitman, 1998). Finally Simon and VonKorff (1998) 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. Severity may well be a confounding factor here, but the low rates for suicide, compared with the common estimates, are notable.

Jick, Dean and Jick (1995) studying 200,000 exposures to antidepressants in primary care in Britain reported a suicide rate of 68/100,000 exposures. These figures derive largely from patients treated with pre-SSRI antidepressants who can be presumed to have been in the main more severely depressed than patients on SSRIs.

In a second study from primary care in Britain looking at suicide attempts on paroxetine, fluoxetine, amitriptyline, and dothiepin, Jick, Kaye and Jick (2004) reported that when dothiepin was used as the reference compound there was no difference between these agents. However, when amitriptyline was used as the reference compound, the figures for dothiepin were 1.21 (95% CI: 0.89–1.64), for fluoxetine

1.46 (95% CI: 1.03–1.91), and for paroxetine 1.55 (95% CI: 1.11–2.16) (FDA, 2004).

A further study utilizing the general practice research database in New Zealand has found that tricylic usage was associated with a rate of 68 suicides per 100,000 persons exposed to treatment (Didham, McConnell, Blair & Reith, in press). In contrast, exposure to SSRIs led to 111 suicides per 100,000 patients exposed.

Finally, utilizing a database of 2.5 million person years and 212 suicides from North Staffordshire, Boardman and Healy (2001) 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 that are compatible with observed national rates of suicide in the UK. The Boardman and Healy study gives a figure of 27/100,000 patients per annum as the likely rate for the primary care primary affective disorders component of the suicides stemming from all mood disorders.

These figures from the DSRU, and other studies, map closely on to the figures stemming from RCTs submitted to regulators, which yield figures of 180 suicides per 100,000 patients exposed to active treatment compared with 67 suicides per 100,000 patients exposed to placebo (Healy & Whitaker, 2003). But if these figures are correct, surely they would lead to an increase in national suicide rates, which in some countries have fallen over the past 20 years (Gunnell & Ashby, 2004). The quantification of treatment-related risks is explored below.

The IMR model system

These epidemiological studies offer some translation into clinical practice from the cross-sectional estimates that come from randomized controlled trials. In order to determine the possible numbers of treatment related suicides, any model will need an estimate of the number of people who are at risk amongst those being treated. While there is excellent data on the number of prescriptions and quantity of medication issued in the USA and the UK for all formulations of antidepressants, there is no recognized method of establishing how many patients have in fact been treated. This has led one of us (GA) to design a model, which translates quantities of medication doses into numbers of patients.

This model is based on profiles of dropout rates from treatment taken from the Drug Safety Research Unit studies in Southampton (MacKay et al., 1998). These studies of SSRIs indicate characteristic patterns of patient usage or tolerance, from the early weeks through to several years of usage. The total quantity of medication issued has been obtained from the Department of Health in England and from IMS Health in the USA.

An accurate method has been devised for converting the progressive consumption of medication, moderated by patient usage, into actual numbers of patients. This has led to the construction of a model called Investigative Medication Routine (IMR). The IMR starts running from the year of introduction of the drug and generates an image of the patient growth and flow that is progressively updated, providing all the accumulating totals of those joining or leaving the drug as the years go by for the developing national cohort.

The model logic, arithmetic, assumptions and implementation have been challenged in a series of stress and sensitivity tests, designed to expose errors, benign assumptions and to measure model response to variation of input parameters. Independent assessments have been made at two UK Universities and by the British regulator (MHRA/CSM). No flaws in the logic and methodology of the IMR patient flow model system have been found to date.

In summary, the IMR will calculate any patient subtotal for any year and for the whole term of new patients, total patients treated, current long-term patients, dropout patients (both short- and long-term), new long-term patients, and with input from clinical trial data the numbers of treatment induced suicides. A more detailed description is in preparation.

Patient flow

Annual cohorts can be characterized individually within the model, with a different usage profile, dropout rate, (e.g., patient cohorts in 2003 may have had a different composition by indication to those in 1993). The IMR model specifically identifies the steady growth of long-term patients who will progressively use more and more of the medication issued in any one year. It will also give breakdowns of how many patients have been on drug for a given number of years. For example, using the patient usage profiles from the DSRU studies, the IMR yields the following patient figures for fluoxetine, sertraline and paroxetine usage in the US and UK from the point of launch—see Tables III and IV.

Prescriptions, pills and patients

For SSRI cohorts, the IMR demonstrates the complex relationship between prescriptions, pills and patients. Figure 3 shows that, in England, as the cycle develops, the requirement for medication increased by an average 42 million pills or doses/year;

Table III. IMR: development of new and long-term patients in England/UK for fluoxetine, paroxetine and sertraline.

	Annual new patients				Development of long term patients			
Year	Fluoxetine	Paroxetine	Sertraline	Total	Fluoxetine	Paroxetine	Sertraline	Total
1989	21,560			21,560	–			–
1990	46,067			46,067	4,312			4,312
1991	72,119	18,218	10,710	101,047	13,267	–	–	13,267
1992	124,420	93,867	38,294	256,581	26,651	3,644	2,142	32,437
1993	161,924	106,501	43,546	311,971	49,203	22,198	9,672	81,073
1994	222,244	112,169	69,044	403,458	77,176	41,961	17,680	136,818
1995	310,485	172,220	99,704	582,410	114,307	60,638	29,890	204,835
1996	314,353	269,450	104,505	688,308	165,354	89,151	47,073	301,578
1997	359,564	302,989	110,406	772,959	212,108	139,799	63,522	415,428
1998	260,586	268,372	97,288	626,246	262,340	193,237	79,234	534,811
1999	280,586	300,919	73,485	654,990	287,291	233,090	90,508	610,890
2000	288,981	282,682	122,398	694,061	312,061	268,846	95,512	676,418
2001	362,058	341,193	125,979	829,231	335,777	296,732	109,412	741,920
2002	319,547	244,518	147,428	711,493	371,363	327,385	122,947	821,695
2003	268,366	82,886	122,722	473,973	395,053	284,877	139,191	819,121
Total					Total for 2003			
Eng.	3,412,861	2,595,984	1,165,510	7,174,354	395,053	284,877	139,191	819,121
UK	4,162,026	3,165,834	1,421,353	8,749,213	481,772	347,411	169,745	998,928

The UK results are scaled from the results for England by the population factor of 0.82.

Table IV. IMR: development of new and long-term patients in the USA for fluoxetine, paroxetine and sertraline.

	New patients starting on drug in current year				Development of long term patients			
Year	Fluoxetine	Paroxetine	Sertraline	Total	Fluoxetine	Paroxetine	Sertraline	Total
1988	899,856			899,856	0			0
1989	1,547,442			1,547,442	179,971			179,971
1990	1,947,338			1,947,338	478,661			478,661
1991	426,619			426,619	829,259			829,259
1992	1,787,521		213,790	2,001,310	838,440		0	838,440
1993	1,020,216	850,205	2,373,784	4,244,205	1,100,451	0	42,758	1,143,209
1994	2,863,022	1,467,859	1,677,421	6,008,302	1,193,890	170,041	514,949	1,878,880
1995	2,280,438	1,289,065	2,171,122	5,740,625	1,635,470	453,410	817,125	2,906,006
1996	2,328,614	1,653,982	1,940,201	5,922,796	1,929,658	674,428	1,173,424	3,777,510
1997	2,622,047	2,106,261	1,675,933	6,404,241	2,191,187	939,762	1,446,706	4,577,655
1998	2,663,209	2,037,645	2,106,666	6,807,520	2,480,597	1,268,091	1,631,571	5,380,258
1999	1,855,358	1,861,142	2,068,905	5,785,404	2,747,032	1,548,724	1,877,227	6,172,982
2000	1,380,479	2,330,549	2,292,718	6,003,747	2,820,418	1,759,557	2,091,020	6,670,995
2001	1,610,645	1,887,306	2,463,645	5,961,595	2,780,328	2,036,854	2,323,468	7,140,650
2002	1,805,015	3,046,058	3,041,536	7,892,609	2,785,383	2,197,859	2,564,894	7,548,136
					Total for 2002			
Total	27,037,820	18,530,071	22,025,721	67,593,612	2,785,383	2,197,859	2,564,894	7,548,136

this arose primarily from the demand by an increasing number of long-term patients (LTP) on chronic treatment rather than from an increasing number of new patients entering treatment.

Figure 4 translates medication doses of paroxetine, fluoxetine and sertraline into patients and demonstrates that the number of new patients is not a simple proportional function of the scripts and pills issued. In fact the number of new patients tends to stabilize at around 300,000 per year for all three pills combined. The distribution of medication between new and long-term patients is shown in Figure 5. By 2003, new patients only use 18% approximately of the medication issued for these three drugs.

Suicide submodel

There is clear evidence that the risk of induced suicide or suicidal acts occurs at a many fold greater rate at times of antidepressant dose transition, such as in the first weeks of starting (Jick et al., 2004), or during discontinuation (Glaxo SmithKline, 2003). The IMR system contains a submodel that operates on the number of patients starting or leaving the drug

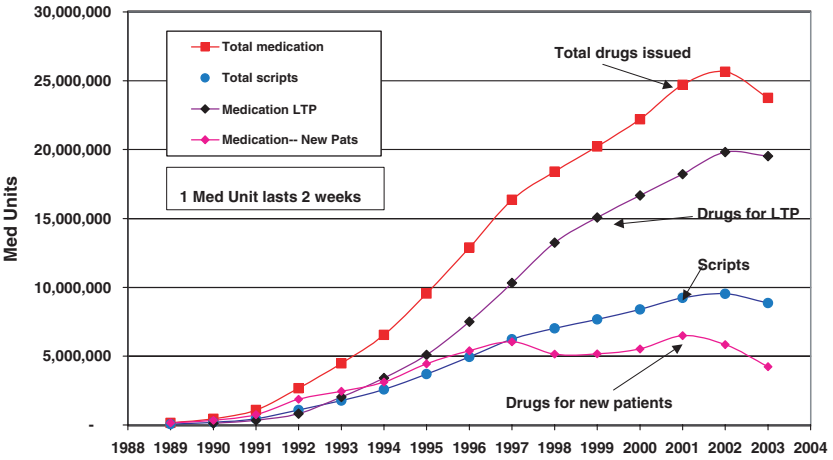

Figure 3. IMR: Consumption of medication, distribution between new patients, long-term patients and prescriptions in England (paroxetine, fluoxetine and sertraline).

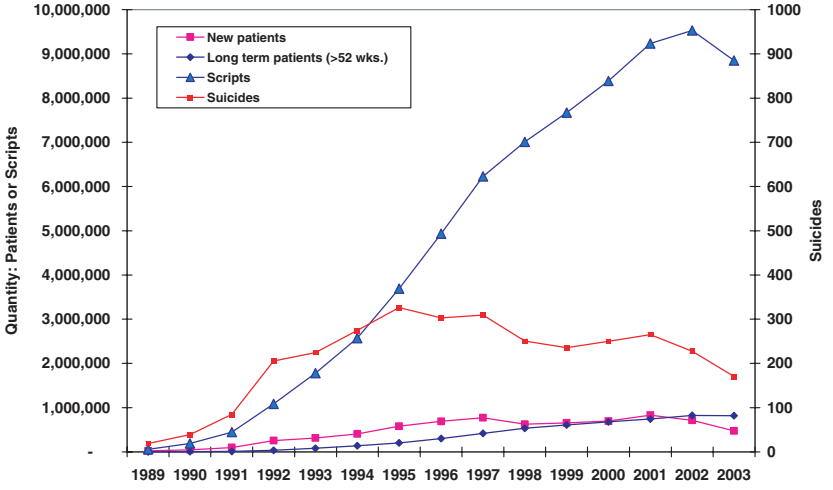

Figure 4. IMR: Development of new and long-term patients, scripts and suicides in England for paroxetine, fluoxetine and sertraline.

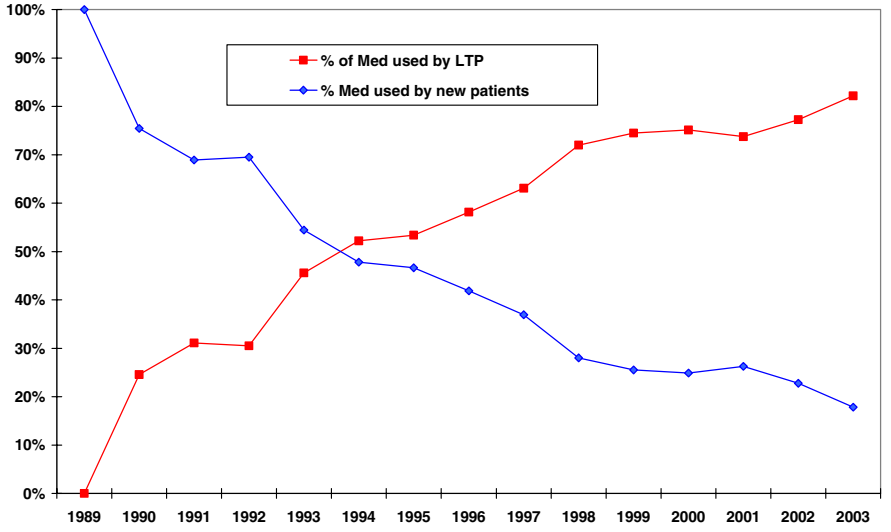

Figure 5. IMR: Relative distribution over time of medication between long-term patients and new patients in England for paroxetine, fluoxetine and sertraline.

Table V. IMR: suicide submodel showing a varied depression anxiety ratio over time, (average 25%) with estimates of suicides and effect on national suicide rate for fluoxetine, paroxetine and sertraline in England.

	New pats at risk (3 Drugs)	Dep. %	Anx. %	Total depressed	Est. suicides	Contrib. to Nat rate Sui./100 K
1989	21,560	80	20	17,248	19	0.04
1990	46,067	75	25	34,550	39	0.08
1991	101,047	75	25	75,785	85	0.18
1992	256,581	70	30	179,607	205	0.43
1993	311,971	60	40	187,183	225	0.47
1994	403,458	55	45	221,902	274	0.57
1995	582,410	40	60	232,964	326	0.68
1996	688,308	25	75	172,077	303	0.63
1997	772,959	20	80	154,592	309	0.64
1998	626,246	20	80	125,249	250	0.52
1999	654,990	15	85	98,248	236	0.49
2000	694,061	15	85	104,109	250	0.52
2001	829,231	10	90	82,923	265	0.55
2002	711,493	10	90	71,149	228	0.47
2003	473,973	15	85	71,096	171	0.36
	7,174,354			1,828,683	3185	

Table V models the three drugs in England. The contribution to national rate for the UK is the same as given here due to the cancelling of population scaling factor in the upgrading calculation.

to calculate rates of suicide. Using data from clinical trials, we present figures here for patients new to treatment to provide estimates for the number of excess suicides that may have occurred.

It is recognized that SSRI antidepressants have been prescribed for an expanding set of indications, from depression to mild anxiety, social phobias, and other conditions each of which carry different baseline rates of suicide prior to treatment. The suicide submodel allows each annual cohort of new patients to have a different composition of conditions, each with individual risk rates. Currently, for simplicity, only two conditions, depression and anxiety, are used to define the limits of the range. Thus the possible suicides in cohorts with any chosen depressed/anxiety (D/A) profiles ranging from 100% depressed to 100% anxious can be calculated. In addition, the D/A profiles may be modified annually over the life of a drug to match the changing profile of patient risk caused by the extension of indications for which SSRIs are prescribed.

The importance of this flexibility may be illustrated by considering various possible patient cohorts. For instance, the actual patients treated may show a higher proportion of women than men compared with the clinical trials from which the original risk estimates are drawn, or a higher proportion of minors, or of patients suffering from anxiety disorders, or fatigue syndromes stemming from infectious disorders. The corresponding baseline rates for suicide in each of these populations will be lower than for depressive disorders, thus lowering the baseline rate of suicide in the overall cohort. However, based on the analysis by Fergusson et al., outlined above, the relative risk from active drug treatment in the early phase of treatment over baseline (placebo) appears to remain approximately the same for other conditions as for depression. The IMR model can be configured to track any such mix of conditions per annual cohort.

In the worked example here, the IMR used excess suicide rates over placebo from Table I, which yields 168–64 or 104 suicides/100,000 depressed patients treated and a baseline rate of suicides for anxiety of 20/100,000 patients, multiplied by an odds ratio of 2.2 derived from Fergusson et al., to give an excess rate suicides for anxiety of 24/100,000 patients. We have assumed that the proportion of patients being treated for anxiety indications has progressively grown over time, leading to a declining percentage of depressed patients. Various estimates can be made, but the example here gives proportions of 25% and 35% depressed patients over 12 years (Table V, Figure 6).

Effect of antidepressants on national suicide rates

It has been argued that SSRI usage cannot induce suicides in line with the rates found in RCTs and other studies cited here because the continuing growth of scripts issued has been accompanied at least in some instances by a fall in suicide rates. This is an intuitively appealing argument. However, the IMR makes it clear that the massive growth in SSRI usage does not translate into a growth of new or at risk patients. There is in fact a complex relationship (that changes annually) between scripts, pills and patients, and scripts are not synonymous with patients at risk; this is outlined in Figures 3

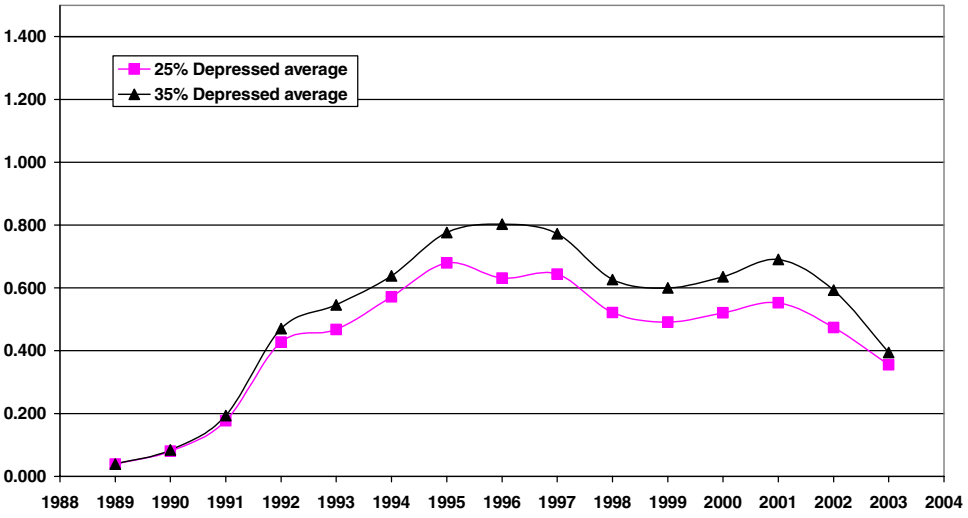

Figure 6. IMR: Contribution of estimated SSRI suicides per 100,000 population for two cohort depression mixes (25% and 35%) in England for paroxetine, fluoxetine and sertraline.

and 4. Without the IMR or a similar tool these dynamic relationships cannot be investigated or quantified.

The potential contribution of SSRI-induced suicides from these three drugs to the national rate is shown in Figure 6 for two cohorts with differing depression/anxiety mixtures. Assuming a population for England of 48 million, a cohort in which over time 25% of the treated patients who were depressed will add to the national suicide rate an increasing contribution due to the three SSRIs from 1991 rising to 0.68 of a suicide/100,000 of national population by 1995. Thereafter, a changing new patient mix gives rise to a slowly declining contribution to total suicides despite the fact that both scripts and pills continue to increase dramatically. The IMR figure of an excess of suicides of 228 on the three major SSRI antidepressants for England in 2002 is compatible with Gunnell and Ashby (2004), who have argued that projected figures of 388 suicides stemming from antidepressant usage can be accommodated within national rates even when these are in decline. Based on this, it would seem that any investigation of the effect of SSRIs on national suicide rates should focus on the period from 1988–1995.

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