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Safety of Antidepressants in Pregnancy With Particular Reference to Paroxetine (Paxil)

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Background

In recent years there has been a marked shift among many academic clinicians, primarily in America, toward advocating the detection of nervous disorders in pregnant women and a treatment of these disorders with antidepressants, especially serotonin reuptake inhibiting (SSRIs) antidepressants, where before there would have been much greater caution in using such treatments.

It seems likely that this shift stems from the marketing efforts of pharmaceutical companies, and perhaps GlaxoSmithKline (GSK) in particular, who have sought to make paroxetine (Paxil) the antidepressant of choice for women, including women of child-bearing years.

This marketing to women of child-bearing years took shape around 1997 in response to an initiative by Lilly for fluoxetine (Prozac) that discredited both Paxil and Zoloft in advertising campaigns, as well as in academic symposia, and articles in academic journals delivering a message that Prozac was much less likely to cause physical dependence and withdrawal than Paxil.

SmithKline Beecham's initial response was to claim that the short half-life of Paxil meant that women contemplating pregnancy would be able to get off treatment more readily than they would be able to get off Prozac.

This initial response was subsequently developed into a marketing position that Paxil was the antidepressant of choice for women of childbearing years. It was presented as a treatment for Premenstrual Dysphoric Disorder (PMDD), as well as for the hot-flashes and depressive symptoms that accompany the menopause, and in particular for women who were pregnant or likely to become pregnant, claiming that they could get off treatment readily if wish,, and in addition concentrations of the drug were low in breast milk and therefore this was a suitable treatment for women during the postnatal period.

There were two key aspects to this marketing campaign; direct to consumer advertising aimed to drive women in the reproductive years to physicians to request Paxil for their treatment, and a sophisticated multifaceted marketing campaign to physicians with the aim of increasing prescriptions for Paxil to women for a range of situations – depression and anxiety, premenstrual dysphoric disorder, social anxiety disorder as well as in pregnancy and lactation. In these ways, the marketing targeted one of the most vulnerable groups of the population – mothers and their unborn babies.

In implementing this marketing, GlaxoSmithKline have supported educational programmes advocating a detection of depressive disorders in women of child-bearing years that have downplayed the risks associated with treatment. These risks include major birth defects and in particular cardiac defects, spontaneous abortions (miscarriage) as well as pulmonary hypertension, pre-term birth, low birth weight, neonatal withdrawal syndromes and an increased rate of voluntary abortions. An extensive direct to consumer marketing

campaign was mounted raising awareness and encouraging women to self diagnose and present to their doctor with a range of psychological symptoms labelled as anxiety, depression, social anxiety disorder and premenstrual dysphoric disorder.

A substantial change in the culture of clinical care and prescribing for pregnant women has been effected.

This paper will cover the issues of the nature of the evidence for treatment with an antidepressant during pregnancy. It focuses on Paxil, but there are comparable risks associated with other SSRIs and a number of related medicines.

Medical professionals have a particular duty of care to women of child-bearing years in relation to informed consent when the possibility of starting an antidepressant is raised. This duty requires women to be informed of two risks. First there is a risk they may become physically dependent on these drugs, in a manner that may later make it very difficult to stop treatment once they are pregnant or contemplating a pregnancy. Second, there is a risk that treatment may induce major birth defects in addition to leading to a number of other problems.

1 Do The Antidepressants Bring Benefits to Pregnancy?

This paper is written from the point of view that antidepressants work, but that their benefits are less substantial than is commonly thought. There are no specific trials of antidepressants in pregnancy, so evidence for benefit is extrapolated from the general adult population.

Our best data on the evidence for benefits from antidepressants come from an investigation undertaken in 2006 by the American Food and Drug Administration, who assessing the risks of suicidality on antidepressants, asked companies for all placebo controlled trials undertaken in depression. They received data from trials that had enrolled over 100,000 patients (1).

In brief these trials demonstrated that 5 out of every 10 patients recruited "responded" on the outcome measure used in the trial, a physician rated disease specific rating scale, while 4 out of 10 responded to the placebo on the same measures.

However, there are a number of ambiguities in the word "works" as applied to these findings. First, these results are not convincing evidence the drugs work. They are even less convincing if it is taken into account that rating scales other than physician rated depression specific rating scales were used in these trials, such as quality of life scales completed by patients, but the data using these other rating scales has remained largely unpublished and was not analysed by FDA. Had it been analysed, it seems unlikely that any benefit of antidepressants would have been shown on these scales.

Second, on measures of efficacy such as the numbers of dead bodies in the active treatment arm compared with placebo, there are a greater number of dead bodies in the active treatment arm of antidepressant trials than there are in the placebo arm. In other words, on meaningful outcome measures that would command general support these treatments have not been shown to work.

Third, the findings indicate that 4 of every 5 people appearing to respond to an antidepressant would have responded to placebo. Up to 80% of the apparent response therefore is down to placebo factors, with only 1 in 10 patients showing a specific response to the active drug.

If clinicians are to practice evidence-based medicine, on the basis of these findings they should resort to non-pharmacological interventions in the first instance, and only turn to antidepressants in refractory cases. Following the evidence in this fashion would in most instances result in patients remaining drug free in the first trimester of pregnancy.

The position we take in this paper coincides with the position adopted by FDA, which is that this data provides at best a signal of possible efficacy, rather than a demonstration of actual efficacy (2).

One of the hazards of the way data from controlled trials of antidepressants is read at present is that signals of possible efficacy are translated into a real use of drug treatments as first line where in fact the evidence would not warrant such an outcome. There has been selective publication of trials, selective publication of data from trials, a great number of the trials as well as opinion pieces published have been ghostwritten. It is likely that this ghostwriting has contributed to a misleading impression of efficacy.

A matter of significant concern in recent years has been the mass screening of pregnant women with rating scales for anxiety and depression, high scores on which are likely to translate into prescriptions of SSRIs.

There is no reason to believe that the results of a controlled trial of antidepressants in pregnancy would yield results significantly at odds with the findings above.

A reasonable clinical approach to prescribing in general should balance the evidence of benefits against that of hazards for a new drug over existing effective medicines or no treatment. The slender evidence for efficacy outlined here needs to be balanced when prescribing in pregnancy against both foreseen and unforeseen fetal harms. The foreseen harms inform all prescribing but given the presence of a third party, the foetus, the possibility of unforeseen harms has underpinned the traditional principle that medications should be avoided in pregnancy if at all possible and in particular in the first trimester where the potential for malformations is the greatest, and because those malformations or other injuries can have devastating and lifelong consequences for both parents and child.

2 The Risks of Leaving Antenatal Depression Unmedicated

It is common to find statements now in the academic literature to the effect that 35% of pregnant women have depressive symptoms and that 10% of them are depressed (3,4). It is also common to find articles and editorials claiming that the consequences of not treating pregnant women with nervous problems with antidepressants far outweigh any adverse effects of treatment (5, 6).

However, one problem with this formulation is that having symptoms, even meeting every single one of the operational criteria for depression, does not necessarily mean a person is depressed. Making a diagnosis in these cases simply on the basis of a symptom tally is a profound clinical mistake.

Many of depressive symptoms arise in states of stress – such as pregnancy. Treating for depression on the basis of a depressive symptom count would return us to the days when medical adverts openly advocated treating hypertensive or asthmatic patients with benzodiazepines as these were supposedly clearly stress related disorders.

When arguments for treating antenatal depression are put forward, they state that untreated depression leads to smoking, alcohol and drug intake, poor self-care, suicide and postnatal depression (5,7). They furthermore infer that there may be a direct toxic effect of untreated depression on the foetus. Finally they point to effects of untreated antenatal depression on the development of the child in later life, arguing that these are substantial and deleterious.

The prevalence of major depression is often overstated in these arguments for treatment. The point prevalence of major depression is (or 'around 4%') 4%, 5% and 3% in the first second and third trimesters of pregnancy (8). This group can be further examined to determine the true hazards of depression in pregnancy.

As a first step here we must distinguish melancholia or what has also been called endogenous depression or a severe depressive disorder with or without psychotic features, from conditions commonly labelled as depressions, anxiety disorders, or mixed anxiety-depressive disorders, or neurotic or reactive depression.

There are no known direct toxic effects of these latter non-melancholic antenatal "depressions" on the foetus. The foetus is isolated from the mother and is comparatively immune to maternal influences, other than infections or drugs that cross the placenta. There is for instance no known endocrine change linked to these common nervous disorders that affect pregnant women that could affect the foetus.

The only psychiatric disorder for which there is any proven endocrine abnormality is melancholia, and even in this case the endocrine disturbances are of a lesser degree to those found in severe physical stress or frank

endocrine disorders, and neither of these states are associated with birth defects.

Melancholia in pregnancy is furthermore rare. The traditional wisdom is that this disorder can arise in pregnancy, but that it very commonly clears with birth, and does not extend into the postnatal period (8). This suggests that such disorders may have a hormonal basis.

In contrast to melancholia, the situation for women when it comes to the less severe nervous disorders more likely to stem from social factors that might be linked to pregnancy would appear to be better now than formerly. Within living memory, pregnancy was the condition most likely to lead to a woman's death, it commonly resulted in immediate post-partum health complications such as infections or haemorrhages and enduring complications such as uterine prolapse, incontinence and other difficulties, babies were often stillborn or died shortly after birth, and the process of labour was uncontrolled so that it might endure for up to a week with little or no analgesia. There was a recognised terror of parturition.

As regards the risk of suicide noted above, suicide is a highly culture specific disorder. The management of this risk should therefore vary from culture to culture. The data on the frequency of suicide in pregnancy is of extremely poor quality, but there are indicators that suicides have fallen in recent decades in the West, with suggestions that in part at least suicide was a response to a problematic pregnancy (8). If suicide in pregnancy is commonly a response to a problem posed by a pregnancy, an antidepressant would seem unlikely to offer a good answer, especially as in placebo controlled trials of antidepressants there are more suicides in the active treatment arms of these trials than in the placebo arms (3).

As regards the risks of substance abuse stemming from untreated depression, if there were evidence that depressed women take up drinking or smoking early in pregnancy, where they had been abstinent before, there might be a case for ensuring that depression was treated even if that involved medication. But there is no such evidence. There is also no evidence that the treatment of substance abuse that has an onset in pregnancy shows a response to antidepressants. In either the case of women with established smoking and alcohol abuse or onset during a pregnancy, we have no data on the risks of combining the hazards of smoking, alcohol, or other substance abuse and antidepressant intake, if antidepressant intake does not lead to an immediate cessation of these other substances.

The foetus does not distinguish between prescription and non prescription medicine in terms of effects and nor, for that matter, does the mother. In the case of substance abuse in general, the key issue is whether the risks of teratogenesis are greater with agents like paroxetine or fluoxetine than with cocaine or smoking for instance. Laboratory studies outlined below now indicate that the risks of birth defects on an SSRI like Paxil are greater than with a serotonin reuptake inhibitor such as cocaine (9).

Postnatal depression does have effects on the bonding between mother and child and does affect the physical and mental development of the child, leaving them prone to affective instability in later life and with impaired cognitive performance relative to their peers in childhood (8). There is however no evidence that antenatal depression does this.

In addition, the link between antenatal and postnatal depression is overemphasized. While first trimester depression is a risk factor for post natal depression, most (71%) first trimester depression does not go on to post natal depression and most (64%) post natal depression is not associated with first trimester depression (10). If antenatal depression leads to a postnatal depression, there is always the opportunity to treat the depressive disorder vigorously in the postnatal period.

In the event that it is thought that a particular antenatal depression or anxiety state needs active treatment rather than simply judicious monitoring and hygienic measures, there are treatments other than antidepressant drugs. For mild to moderate depressions, there are interpersonal therapy (IPT) and cognitive behavioural therapy (CBT), which for conditions of this level of severity are as efficacious as drug treatment and can moreover now be delivered by computer in a cost-effective fashion. Indeed, given the role of social factors associated with the nervous states found in pregnancy, it is worth noting that IPT originated in part as a treatment for postnatal depression that focuses on social and interpersonal issues and that it would appear accordingly to be particularly suitable for antenatal disorders.

For the rare severe or melancholic depressive disorders, treatment options include the use of non-serotonin reuptake inhibiting tricyclic antidepressants or even serotonin reuptake inhibiting tricyclics as the hazards of treatment seem likely to stem from potency of uptake inhibition and the tricyclics are in general less potent serotonin reuptake inhibitors, and these antidepressants rather than SSRIs are recommended by guidelines such as those issued by Britain's National Institute for Health and Clinical Excellence (NICE). Where available, electroconvulsive therapy (ECT) offers a further option.

3 SSRIs & Teratogenesis

Many academic texts, and review articles, and other pronouncements convey an impression that the evidence regarding the risk of teratogenesis is equivocal (1, 2). This is extraordinary given the data, and needs explaining it its own right.

In 2005, GlaxoSmithKline were required by FDA to change the warning label on paroxetine to a pregnancy category D. This change was consequent on a study undertaken by the company in 2005 but only published in 2007 - 2 years later (11).

As of 2008, this study by GSK and 14 other studies had been reported from 1998 onwards (12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26) that

contained paroxetine specific data and were adjudged by GlaxoSmithKline to be sufficiently methodologically sound to include in a meta-analysis (27).

These included case cohort and medical records studies. Overall the studies GSK analysed gave a clear risk of major defects for paroxetine taken in the first trimester with an odds ratio of 1.3 (C.I., 1.1, 1.6) and an odds ratio for specifically cardiac defects of 1.5 (1.2, 1.9). In terms of figures on the risks of overall defects 10 studies gave an increase in the odds ratio of a defect, 3 gave a decrease and 2 returned a relative risk of 1.0. In terms of cardiac defects, 9 studies gave an increase in the odds ratio of a defect, 3 indicated no increase in risk while 1 study returned a figure of 1.0.

(A plot of these studies has been compiled by GlaxoSmithKline and presented on their website. We produce the plot for all major birth defects and for specifically cardiac defects in Appendix 1).

Of the studies that did not support a risk of paroxetine, some indicated a clear risk on other SSRIs (26), while many of the studies pointing to risks with paroxetine also point to risks with other SSRIs.

Two further studies were considered by GSK to be methodologically sound but were not included in the analysis. In one, there was a marked increase of risk for both cardiac defects and major birth defects on antidepressants compared to non-treatment but also an interaction between antidepressants and benzodiazepines (28). In the second, there was no data for specific antidepressants but again an increase in risk with antidepressants compared to non-treatment (29).

Cause and Effect

Some have claimed that the only way that a birth defect could be causally related to antidepressant intake is by means of controlled trials. But in fact there is no basis for the claim that RCTs are necessary for a demonstration of birth defects, and in fact no birth defect has ever been established on the basis of a controlled trial. Indeed, few if any significant adverse effects of a drug, birth defect or otherwise, have been demonstrated by means of randomized trials.

Randomized trials are a subset of epidemiological studies that control for confounding influences by a particular method. This method often allows a much smaller sample of subjects to be recruited, although in this case the sample size is unlikely to be smaller than in a cohort study. While RCTs ordinarily benefit by being able to recruit fewer subjects, they commonly give rise to concerns that the samples recruited to such studies are homogeneous to the point that the findings from such studies may not generalise to typical clinical settings.

Those who argue that current data about the hazards of antidepressants, arising from the studies that have already been undertaken, have not been conclusive offer an argument in defence of their position that hinges around a

particular and incorrect interpretation of point estimates and their related confidence intervals.

Typically the argument is if the 95% confidence interval around the odds ratio for a hazard includes the figure 1.0, there is no risk. This interpretation is wrong.

If the point estimate for the odds ratio is itself 1.0 or shifted to the left of 1.0, there is unlikely to be a risk – but still could be a risk. But if the point estimate lies to the right of 1.0, there is likely to be a risk, and if a large majority of studies using different methods find an equivalent shift to the right, as GlaxoSmithKline have found, then it is highly likely there is an increase in risk.

If the data are shifted to the right, but the 95% confidence interval still includes the figure 1.0, this does not mean there is no increase in risk – it is more likely to mean the study is underpowered or there are factors others than a simple undifferentiated risk in all those exposed to treatment.

This can be brought out by a thought experiment. Assume a doctor is forced to put a patient, likely to become pregnant, on one of two drugs for a particular clinical condition, both of which come with a risk of birth defects. If drug A has an odds ratio of 1.8 with a 95% confidence interval stretching from 1.1 to 2.5, and drug B comes with an odds ratio of 5.4 with a 95% confidence interval stretching from 0.92 to 25.2, the drug to recommend the patient should take is drug A rather than drug B. The data suggests drug B is likely to be three times riskier than drug A.

Against this background, consider the question of when the epidemiological data began to point conclusively to the existence of a risk of birth defects. As of 2002, there were 4 studies available. The Kulin study from 1998 (12), which pointed to an odds ratio of a birth defect on paroxetine compared to non-treatment of 1.8 (95% C.I., 0.6, 5.4).

Second, a further study that appeared in 2001 from Unfred and colleagues (13) showing a rate of major malformations of 4.2% Paxil vs. 0.05% for controls. This is a greater than 8-fold increase in risk on Paxil. This study has remained unpublished as of 2009.

Third, another study that appeared in abstract form in 2002 from Diav-Citrin (30) and colleagues in 2002 that had a rate of 3.9% for major malformations on paroxetine vs. 2.1% in controls. This study was only published in 2005.

Fourth a study by Simon et al (14) which showed an odds ratio of major malformations for paroxetine of 0.7 (95% C.I. 0.0, 13.5).

Combined these studies and the consistency between them as of 2002 made a strong case that there was a real increase in risk. In part this evidence of risk may not have come to wider attention because 2 of the 4 studies as of 2002 were unpublished and 1 remains unpublished.

The Kulin et al (12) paper also reports an excess of therapeutic and spontaneous abortions on treatment. Combining the data offered for spontaneous and therapeutic abortions gives 20.2% on SSRI versus 12.7% for controls; an odds ratio of 1.7 (95% CI 1.1, 2.9). In the case of spontaneous abortions alone, the figures are 13.5% compared to 8.9% for controls; an odds ratio of 1.6 (95% C.I., 0.9, 2.9).

When data on spontaneous abortions are reported in the cohort studies cited above, they consistently point to an excess in women taking antidepressants. If spontaneous abortions are linked to a greater frequency of birth defects than term births, as is commonly suggested, then the true rate of birth defects linked to antidepressant intake seems likely to be substantially greater than estimates based on term births only.

Causality in the Laboratory

When assessing causality, it is traditional to marry epidemiological with mechanistic or laboratory studies. When the issue involves a birth defect, such studies are usually undertaken in animal populations.

It has been known for 40 years that serotonin has a trophic function in embryogenesis, regulating cell migration in tissues such as the embryonic gut, heart and nervous system (31, 32, 33, 34, 35). Despite this, as of 2009 there had been no rigorous published studies looking at the possible teratogenic effects of SSRIs.

In 2009, a study covering this issue was published (9). It is worth considering the origins of this study. The researchers were working for Schering-Plough who had bought Organon and in the process acquired several SSRIs. As part of work to establish whether these could be brought to the market they undertook a detailed study to compare the teratogenic potential of these drugs with a series of SSRI antidepressants on the market, along with other serotonin reuptake inhibitors such as cocaine and drugs with a known teratogenic potential.

This study demonstrated clear teratogenic effects for a number of antidepressants, in particular serotonin reuptake inhibitors, and especially with paroxetine (9). The findings for paroxetine were dose-related and consistent with what is known of the trophic effects of serotonin in the development of the embryo. The signal was stronger for paroxetine than for other serotonin reuptake inhibitors such as cocaine, and equivalent to known teratogens such as retinol.

The findings from this laboratory study are consistent with the pattern of defects that have emerged in epidemiological studies in recent years. The study led Schering-Plough to abandon the development of their SSRIs, even though the problems seen with these molecules were of a lesser severity than the problems seen with Paxil.

At present the data is best explained in terms of potency of action on the serotonin reuptake site. This suggests the problems may be dose dependent,

for which there is some evidence (22). If an action through serotonin systems is the mechanism through which these drugs pose a risk, then all tricyclic antidepressants that inhibit serotonin reuptake pose some risk, perhaps dependent on dose, as do many antihistamines.

It appears from this study that paroxetine and many other antidepressants are likely to pose a greater risk than for instance drinking alcohol in moderation. The traditional method of handling the risks posed by alcohol has been to encourage women to abstain completely from alcohol while pregnant – which seems diametrically the opposite position to that advocated by those supporting a use of antidepressants in pregnancy.

4 Other Hazards

Aside from teratogenic effects outlined above, there is now a consistent body of evidence linking antidepressants with prematurity, as well as low birth weight (36, 37), and pulmonary hypertension (38) when given in the course of pregnancy.

These problems appear independent of any depression or nervous disorder. A study with a large sample size (n = 1451) found that children of mothers who take SSRI antidepressants for depression appear to have worse outcomes than those of mothers with depression who do not take antidepressants in terms of birth weight and respiratory distress even when maternal illness severity was accounted for (28).

Finally, there is little dispute that antidepressants can trigger a neonatal withdrawal syndrome after birth. This was first noted in 1972 (39). The risk seems most clearcut in the case of paroxetine, for which there has been a greater number of reports to regulators of dependence and withdrawal effects than for any other psychotropic drug, both in those taking the treatment and in neonates (40, 41, 42, 43, 44, 45, 46, 47, 48, 49). While in some cases, this syndrome is mild, it can also be serious leading to convulsions and necrotizing enterocolitis.

At present, in addition to an excess of spontaneous abortions on SSRIs there also appears to be an excess of voluntary abortions. This seems unlikely to stem from women believing their child might have been injured by treatment as almost all expert sources claim that no such injuries happen.

It is surprising that there appear to be no efforts to determine what might underpin this excess. In some cases gross abnormalities may have been revealed on scan. A further possibility lies in the profile of effects of SSRIs. These are anxiolytic agents and this anxiolysis leads in some instances to profound disinhibition, accompanied by impulsive behaviour, where the subject is heedless of the consequences of their actions in a manner quite at odds with their normal personality (50). This is particularly likely to be the case when combined with alcohol.

A further issue to consider is the growing body of evidence that abortions, whether spontaneous miscarriages or voluntary terminations, may increase the risk of subsequent mental health problems, including substance abuse (51, 52). If Paxil has as large an effect on spontaneous miscarriage and abortion rates as it appears to have, these miscarriages and abortions may be laying the basis for a considerable amount of future problems with substance misuse.

5 Antidepressants & Withdrawal

Any question of the possible teratogenic effects of antidepressants needs to take into account the physical dependence that all antidepressants can cause, but SSRIs cause in particular and within the SSRI group paroxetine and venlafaxine do to an even greater extent than others. Some background on the history of dependence on Paxil is attached in an Appendix2.

The specific problem that dependence on Paxil and related drugs causes as regards birth defects is that women of child-bearing years put on these drugs are commonly not informed that they may become dependent on treatment and may be unable to get off treatment or that the treatment may induce major birth defects, as well as pulmonary hypertension, preterm birth, low birth weight and a neonatal withdrawal syndrome. Up to one third of women become pregnant by accident. While on treatment therefore many women may end up several months pregnant before they are aware of being pregnant. Even if aware of being pregnant from the day of conception they may not be able to get off treatment in time to avoid a risk of major birth defects.

There is furthermore no understanding of what gives rise to antidepressant dependence syndromes. The advice usually given involves slow tapering. This works for some but in the case of birth defects as noted above it will commonly work too slowly to avoid the risk of birth defects.

In the absence of agreed procedures to manage difficult withdrawal syndromes, an indeterminate number of women of child-bearing age put on antidepressants will find it difficult or impossible to stop treatment should they wish to have a drug-free pregnancy.

6 Changing Therapeutic Cultures

The evidence outlined here shows the balance of risks and benefits for Paxil use in pregnancy provides no support for its use in this clinical situation and little support for the use of other antidepressants. But current clinical practice and opinion is increasingly at odds with the evidence. How did this situation come about?

Until very recently, the standard clinical view was that all medicines, including antidepressants, should be avoided in pregnancy, unless there was a clear clinical need. While older textbooks still offer this view, there are few recent studies or reviews in mental health and related journals that point to the existence of hazards of treatment or argue against treating antenatal nervous

conditions with antidepressants. Given the clear evidence of risks stemming back almost a decade, and given that following the currently available evidence as regards the benefits of treatment would suggest not medicating too quickly, this switch in treatment philosophy calls for an explanation in its own right.

There is convincing evidence that a number of the reviews in this domain advocating treatment or denying hazards of SSRI have been published under strong influence of pharmaceutical companies. Some papers have been ghostwritten (53) or commissioned by companies (54) , or have been written without the competing interests of their authors being revealed (55). It is also clear that many of the leading figures in women's mental health, at least in the United States, have been heavily sponsored by pharmaceutical companies (56). This undermines the ability of physicians to assess in a reasonable way the available information about these products in order to make the best decisions for their patients

Quite recently there was controversy surrounding the use of antidepressants for children. At the time the controversy blew up, the vast amounts of literature appears to have been written by either company personnel or medical writers, even though in a number of instances it was published under the names of distinguished academics. There was an almost complete mismatch between what the data from studies actually demonstrated when it was possible to get access to this data and what it was claimed in academic literature and meetings these studies had shown.

There appears to be a close to comparable situation in the domains of dependence on and birth defects linked to the use of SSRIs with companies like GlaxoSmithKline having interacted with academics to engineer an extraordinary change in the culture of clinical care. It is all but impossible to know the full extent to which the sources of information relied upon by physicians has become adulterated by the influence of companies.

To avoid harm to women of child-bearing years and their children by restricting the use of antidepressants to these women, we suggest that prior to starting treatment it should be mandatory to inform all women of the risks that treatment may induce major birth defects, miscarriages and other hazards and also of the risk of dependence on these drugs that might lead to an inadvertent or unavoidable involuntary exposure of the unborn child to the risks stemming from its mother's medication.

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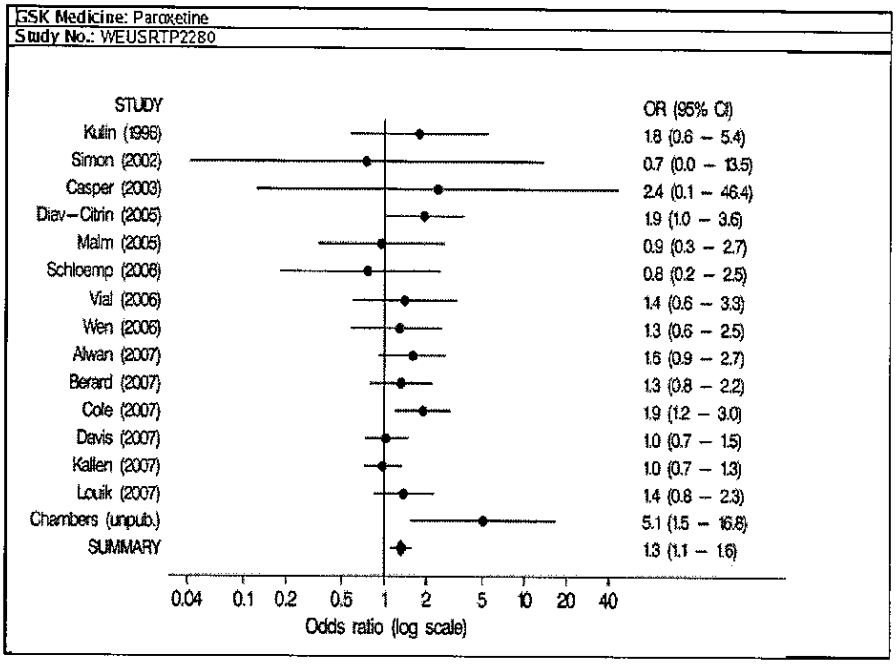
APPENDIX 1

RISK OF MAJOR BIRTH DEFECTS ON PAROXETINE



RISK OF MAJOR CARDIAC DEFECTS ON PAROXETINE

GSK Medicine: Paroxetine
Study No.: WEUSRTP2280

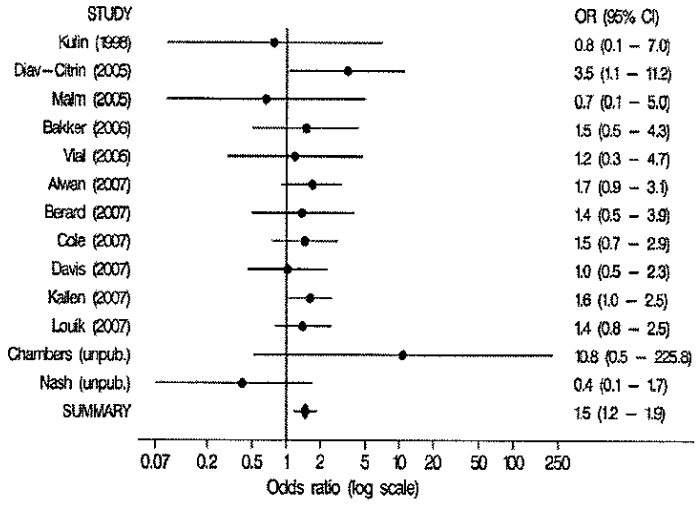


Table 6: First Trimester Paroxetine Use and Cardiac Malformations: Main and Sensitivity Analyses of Overall Homogeneity and Funnel Plot Symmetry

APPENDIX 2:
Dependence on & Withdrawal from Paxil

From the mid-1980s, in the course of their development work with Paxil, Beecham Pharmaceuticals/SmithKline Beecham noted the occurrence of problems on withdrawal from this drug. By the mid-1980s, the company was aware of these problems, having been informed of the problem by senior figures in the field and having undertaken their own healthy volunteer trials.

For example, Professor Peter Tyrer, current editor of the British Journal of Psychiatry, and head of department in University College London, and a clinical triallist for SmithKline Beecham in the early 1980s, reported to the company that treatment with Paxil seemed to entail a significant risk of dependence. The following is from a broadcast interview from October 2004 with Professor Tyrer on BBC's Panorama program:

PT: After the trial ended they said, 'can we continue on these tablets because we feel we've got to have them because they seem to be so effective', but more concerning.. what was of more concern to us was the fact that they were saying, 'I cannot tolerate the symptoms when I stop it'.

SJ: As far as you were concerned then, were these people dependent on Seroxat? [The British trade name for Paxil]

PT: They were showing, yes, signs of dependence.....after only 6 weeks.

SJ: Some of the withdrawal effects were very disturbing.

PT: They also felt more anxious, they felt this feeling of dysphoria, the feeling of being depressed, and in some cases entertaining suicidal thoughts... Yes, it is serious ... we were led to believe that these drugs were particularly effective against suicidal thoughts, and therefore having them at any stage during the course of treatment even.. .and on withdrawal, was a matter of great concern.

SJ: Professor Tyrer didn't investigate these problems any further at the time, but he did tell GlaxoSmithKline what he'd found. He says they weren't very interested.

PT: It was very.. um.. important to concentrate on the positive, so we didn't expect that they would rush in and investigate this problem as a matter of priority.

SJ: And as far as you're aware they didn't investigate the problem?

PT: No.

SJ: We asked GlaxoSmithKline if further studies were commissioned as a result of Professor Tyrer's findings on withdrawal. They didn't say. What they

did tell us was the company "reviewed reports of such symptoms in all its clinical trials as a matter of course".

SmithKline Beecham had already run a set of healthy volunteer studies, which involved exposing normals to drug treatment for only two to three weeks, in which the protocol monitored symptoms of withdrawal for a week afterwards, although GlaxoSmithKline deny that studies designed to detect withdrawal were ever conducted. Approximately 65% of healthy volunteers exposed for only 2-3 weeks reported problems consistent with dependence and withdrawal, during the week of observation following the study. The commonest symptoms experienced were of depression and anxiety as well as a range of other phenomena such as nightmares, dizziness and problems that were coded under non-specific headings such as asthenia and malaise. These are symptoms indicative of physical dependence on the drug – they overlap heavily with the symptoms produced by benzodiazepine withdrawal for instance. Finally in terms of severity, there are grounds for concern in that the problems on withdrawal recorded in healthy volunteers exposed for only two to three weeks included a suicide.

Despite this evidence when Paxil came on the market in both America and Britain, the warnings about possible withdrawal problems were extremely misleading. For instance in the United Kingdom: "As with any psychiatric medication, it is advisable to discontinue therapy gradually as abrupt or sudden discontinuation may lead to symptoms such as disturbed sleep, irritability or dizziness"[1]. In the United States, prior to 12/14/01, the only reference to withdrawal in the Paxil label was under postmarketing reports, which lists voluntary reports of adverse events in patients that "may have no causal relationship with the drug". The label further states that "There have been spontaneous reports that discontinuation (particularly when abrupt) may lead to symptoms such as dizziness, sensory disturbances, agitation or anxiety, nausea and sweating: these events are generally self-limiting".

These statements need to be read in historical context. In 1991, when Paxil was launched clinicians were actively switching patients from benzodiazepines to SSRIs and one of the primary reasons they offered was that unlike the benzodiazepines, antidepressants in general, including SSRIs, were not addictive or dependence producing. Indeed in what looks like a clear effort to move into the anxiety marketplace, where benzodiazepines had been heavily used, GlaxoSmithKline pursued a policy of profiling Paxil as the anxiolytic antidepressant, and this can only have compounded problems for this group of patients.

Unless, they were more wary or skeptical than the average, primary care physicians and psychiatrists will have confidently brushed off patient concerns on this point, as I and others did at the same time.

Furthermore, despite evidence of the emergence of depressive and anxiety symptoms in healthy volunteers on withdrawal, the SSRI companies were

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1 1990/1991 Datasheet Compendium for Paxil.

very actively pursuing prophylactic studies in the late 1980s and early 1990s in depressed patients who had apparently responded to treatment. This involved clinical trials in which patients who had previously responded to Paxil or Zoloft were re-randomized to ongoing Paxil or placebo. A model was being created and actively marketed that depression was a chronic condition that might need long-term or even lifelong treatment. Against this background the emergence of symptoms on withdrawal was increasingly likely to be interpreted by GPs and others as evidence of a returning illness.

It is clear now that SmithKline Beecham must have known that a certain proportion of these patients re-randomized to placebo, who subsequently complained of depressive and anxiety symptoms, were suffering from withdrawal problems. These withdrawal problems however appear to have been used as a basis for claiming that continued SSRI intake had a prophylactic effect against nervous and depressive problems. Based on this SmithKline sought and have received licenses to make these claims regarding prophylaxis for Paxil.

This has had a very clear consequence for clinical practice. When patients have tried to discontinue treatment, they have commonly found their physician claiming that the symptoms they have had are evidence not of a withdrawal syndrome but of a need to continue with treatment indefinitely, potentially for a lifetime.

Thus there appears to have been a failure by companies to seek and inform regulators of possible problems, and a failure by regulators. Whether the regulatory failure is a simple clinical one of failing to appreciate the possibility of hazards or has involved a more active involvement with companies to bury evidence of problems, as happened in the case of Prozac, Paxil and Zoloft and the risk of suicide these drugs pose, remains to be established publicly.

Whatever the origins of the failure to accurately delineate the problem at the point of initial marketing, the background data, reports from senior clinicians and the outcomes of healthy volunteer studies that point clearly to a problem makes the reports of withdrawal following the marketing of Paxil less surprising than might otherwise have been the case.

From shortly after the licensing of this drug regulators and journals were flooded with reports of withdrawal problems for Paxil. There was an increasing series of articles in the scientific literature[2], and Paxil featured prominently in this literature[3]. These reports featured the words withdrawal

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2 Medawar C (1997). The Antidepressant Web. Int J Risk & Safety in Medicine 10, 75-126.

3 Arya DK (1996). Withdrawal after discontinuation of Paroxetine. Aust N Z J Psychiatry, 30(5), 702; Ayd F (1994). Paroxetine withdrawal symptoms. Int Drug Ther Newsl. 29:36; Barr L, Goodman W, Price LH (1994). Physical symptoms associated with paroxetine discontinuation. Am J Psychiatry 151, 289; Bloch M, Stager S, Braun A, Rubinow D (1995). Severe psychiatric symptoms associated with paroxetine withdrawal. Lancet. 346, 57; CSM/MCA, Current Problems in Pharmacovigilance, Volume 19, February 1993 "Dystonia and withdrawal symptoms with paroxetine (Seroxat),; Dahl M,. Olhager E, Ahlner J (1997). Paroxetine withdrawal syndrome in a neonate. Br J Psychiatry. 171, 391-2; D'Arcy (1993). Dystonia and withdrawal symptoms with paroxetine. International Pharmacology Journal, 7:140; Dominguez RA,. Goodnick P (1995). Adverse events after the abrupt discontinuation of paroxetine. Pharmacotherapy. 15, 778-80; Brauer L, Rukstalis M, De Wit H (1995). Acute subjective responses to paroxetine in normal volunteers. Drug Alcohol Depend. 39, 223-30; Fava M (1998). A comparison of symptoms following treatment interruption: Evidence from a randomized, double-blind trial with fluoxetine, sertraline, and paroxetine. Eur Psychiatry 13(suppl 4), 204-205; Fava GA, Grandi S (1995). Withdrawal syndromes after

and dependence prominently[4]. In the mid-1990s, a number of reviews focused attention specifically on the role of the serotonergic system in withdrawal[5].

It is now clear that the rates at which withdrawal problems have been reported to regulators on this drug exceed the rates at which withdrawal problems have been reported on any other psychotropic drug ever. The Paxil rates greatly exceed rates at which comparable problems were reported for the benzodiazepines. The rate at which problems have been reported in the UK, appears to hold in countries other than the UK also, with the World Health Organization recording a higher rate of reports for both withdrawal problems and dependence on Paxil than for the benzodiazepines (see Tables 1 & 2).

A review of the UK regulators ADROIT database obtained in July 2002 shows that SSRIs and similar antidepressants account for five of the top six drugs for which such reactions have been reported:

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paroxetine and sertraline discontinuation. J Clin Psychopharmacol.15, 374-5; Judge R, Parry MG, Quail D, Jacobson J (2002). Discontinuation symptoms: comparison of brief interruption in fluoxetine and paroxetine treatment. Int Clin Psychopharmacol. 17, 217-25; Keuthen N, Cyr P, Ricciardi JA, Minichiello W, Buttolph M, Jenike M (1994). Medication withdrawal symptoms in obsessive-compulsive disorder patients treated with paroxetine J Clin Psychopharmacol 14, 206-7; Landry P, Roy L (1997). Withdrawal hypomania associated with paroxetine. J Clin Psychopharmacology 17, 60-1; Lane R (1996). Withdrawal symptoms after discontinuation of selective serotonin reuptake inhibitors (SSRIs). J Serotonin Research 3,75-83; Milliken C, Cooper SJ (1998). Withdrawal Symptoms from Paroxetine. Human Psychopharmacology 13, 217-9; Pacheco L, Malo P, Aragues E, Etxebeste M (1996). More cases of paroxetine withdrawal syndrome. Br J Psychiatry 169, 384; Phillips SD (1995). A possible paroxetine withdrawal syndrome. Am J Psychiatry 152(4):645-6; Price JS, Waller PC, Wood SM, MacKay AV (1996). A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. Br J Clin Pharmacol. 42, 757-63; Pyke RE (1995). Paroxetine withdrawal syndrome. Am J Psychiatry 152, 149-50; Reeves R, Pinkofsky H (1996). L'hermitte's sign in paroxetine withdrawal. J Clin Psychopharmacol, 16, 411-2; Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB (1998). Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry. 44, 77-87; Shoenberger D (2002). Discontinuing paroxetine: a personal account. Psychother Psychosom. 71, 237-8; Strickland G, Hough D (2000). Unilateral facial numbness and visual blurring associated with paroxetine discontinuation. J Clin Psychopharmacol. 20, 271-2.

4 Arya DK (1996). Withdrawal after discontinuation of Paroxetine. Aust N Z J Psychiatry, 30(5), 702; Ayd F (1994). Paroxetine withdrawal symptoms. Int Drug Ther Newsl. 29:36; Bloch M, Stager S, Braun A, Rubinow D (1995). Severe psychiatric symptoms associated with paroxetine withdrawal. Lancet. 346, 57; CSM/MCA, Current Problems in Pharmacovigilance, Volume 19, February 1993 "Dystonia and withdrawal symptoms with paroxetine (Seroxat),; Dahl M,. Olhager E, Ahlner J (1997). Paroxetine withdrawal syndrome in a neonate. Br J Psychiatry. 171, 391-2; D'Arcy (1993). Dystonia and withdrawal symptoms with paroxetine. International Pharmacology Journal, 7:140; Fava GA, Grandi S (1995). Withdrawal syndromes after paroxetine and sertraline discontinuation. J Clin Psychopharmacol.15, 374-5; Keuthen N, Cyr P, Ricciardi JA, Minichiello W, Buttolph M, Jenike M (1994). Medication withdrawal symptoms in obsessive-compulsive disorder patients treated with paroxetine J Clin Psychopharmacol 14, 206-7; Landry P, Roy L (1997). Withdrawal hypomania associated with paroxetine. J Clin Psychopharmacology 17, 60-1; Lane R (1996). Withdrawal symptoms after discontinuation of selective serotonin reuptake inhibitors (SSRIs). J Serotonin Research 3,75-83; Milliken C, Cooper SJ (1998). Withdrawal Symptoms from Paroxetine. Human Psychopharmacology 13, 217-9; Pacheco L, Malo P, Aragues E, Etxebeste M (1996). More cases of paroxetine withdrawal syndrome. Br J Psychiatry 169, 384; Phillips SD (1995). A possible paroxetine withdrawal syndrome. Am J Psychiatry 152(4):645-6; Price JS, Waller PC, Wood SM, MacKay AV (1996). A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. Br J Clin Pharmacol. 42, 757-63; Pyke RE (1995). Paroxetine withdrawal syndrome. Am J Psychiatry 152, 149-50; Reeves R, Pinkofsky H (1996). L'hermitte's sign in paroxetine withdrawal. J Clin Psychopharmacol, 16, 411-2

5 Coupland NJ, Bell CJ, Potokar JP (1996). Serotonin reuptake inhibitor withdrawal. Journal of Clinical Psychopharmacology 16, 356-362. Berber MJ (1998). FINISH: remembering the discontinuation syndrome. Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory disturbances, and Hyperarousal (anxiety/agitation) J Clin Psychiatry 59, 255; Black K, Shea C, Dursun S, Kutcher S(2000). Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria. J Psychiatry Neurosci 25, 255-256; Donoghue J, Haddad P (1999) Pharmacists lack knowledge of antidepressant discontinuation symptoms. J Clin Psychiatry 60, 124-125; Drugs and Therapeutics Bulletin (1999). Withdrawing patients from antidepressants. 37, 49-52; Fava G (1995). Holding on: depression, sensitization by antidepressant drugs, and the prodigal experts. Psychother Psychosom. 64, 57-61; Frost L, Lal S (1995). Shock-like sensations after discontinuation of selective serotonin reuptake inhibitors. Am J Psychiatry 152, 810; Haddad P, Lejoyeux M, Young A (1998). Antidepressant discontinuation reactions. BMJ. 316, 1105-6; Haddad P (2001). Antidepressant discontinuation syndromes. Drug Safety 24, 183-97; Haddad P (1999). Do antidepressants have any potential to cause addiction? J Psychopharmacology 13, 300-7; Haddad P, Qureshi M (2000). Misdiagnosis of antidepressant discontinuation symptoms. Acta Psychiatr Scand 102, 466-7; Lejoyeux M, Ades J, Mourad I, Solomon J, Dilsaver S (1996) Antidepressant Withdrawal Syndrome: Recognition, Prevention and Management. CNS Drugs 5, 278-92; Mallya G, White K, Gunderson C (1993). Is there a serotonergic withdrawal syndrome? Biol Psychiatry.33, 851-2

It is clear from these bodies of data that SSRIs are linked to withdrawal problems, and that Paxil is linked to more reports of withdrawal than any other drug in clinical history. The frequency of reporting gives some measure of the severity of many of these withdrawal syndromes. Reporting would not be likely in the event of less severe clinical problems. It must also be remembered that this reporting has taken place in the face of a de facto company denial that there could be any serious problem here, and active company research aimed at portraying any problems as the re-emergence of a depressive illness.

TABLE 1

DRUG	Number of UK reports of Withdrawal reactions
PAROXETINE – SSRI	1281
VENLAFAXINE – SSRI	272
TRAMADOL – Opioid	117
FLUOXETINE – SSRI	91
SERTRALINE – SSRI	81
CITALOPRAM – SSRI	49
ZOPICLONE – Benzodiazepine	44
LORAZEPAM – Benzodiazepine	38
FENFLURAMINE	28
DIAZEPAM – Benzodiazepine	24
NITRAZEPAM- Benzodiazepine	21
BUPRENORPHINE – Opioid	19
BUPROPION	18
CIMETIDINE	18
CLOMIPRAMINE	18
AMITRIPTYLINE	15
BACLOFEN	15
TRIFLUOPERAZINE	14
CLOZAPINE	13
FLUVOXAMINE	13
MIRTAZAPINE	13

Comparable data are on file with the WHO.

TABLE 2

DRUG	WHO Withdrawal reactions
PAROXETINE – SSRI	2003
VENLAFAXINE – SSRI	1058
ALPRAZOLAM – Benzodiazepine	843
SERTRALINE – SSRI	585
FENFLURAMINE	450
FLUOXETINE – SSRI	402
TRAMADOL – Opioid	389
PHENTERMINE	371
LORAZEPAM – Benzodiazepine	282
DIAZEPAM – Benzodiazepine	192
TRIAZOLAM – Benzodiazepine	188

The clinical literature on patients going into withdrawal on SSRIs has given rise to an awareness of a range of novel phenomena, which have variously been described as electric head or electric shock like sensations[8]. The discomfort posed by these and other problems has been extreme so that the patient literature is now replete with accounts of patients presenting themselves to the emergency departments of hospitals suspecting illnesses from strokes through to heart attacks. An indeterminately large number of patients have been investigated in hospital for problems, which may well have been withdrawal related problems. A large number of such patients will have been treated inappropriately for other problems following a mistaken diagnosis made in good faith by physicians unaware of the possibility of Paxil related withdrawal problems.

Based on healthy volunteer and clinical studies, the frequency with which these problems may be happening is a matter for concern. The RCTs undertaken in patients were not designed to pick up problems on withdrawal – unlike the healthy volunteer studies on Paxil for instance which were aimed at detecting problems. In healthy volunteer studies approximately 65% of subjects had some features of withdrawal on discontinuing Paxil. The RCT evidence from patients can best be re-interpreted in the light of these findings as evidence that approximately 25% of patients taking Paxil will have sufficiently severe problems that they will be unable to discontinue without a taper requiring several months of treatment possibly supplemented by substitution of other agents.

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6 Trenque T, Piednoir D, Frances C, Millart H, Germain ML (2002). Reports of withdrawal syndrome with the use of SSRIs: a case/non case study in the French pharmacovigilance database. Pharmacoepidemiology and Drug Safety 11, 281-283.

7 Dallaire S (2003). Withdrawal reactions with paroxetine and other SSRIs. Canadian Adverse Reaction Newsletter 13, issue 2.

8 Medawar C, Herxheimer A, Bell A, Jofre S (2002). Paroxetine, Panorama and user reporting of ADRs: Consumer intelligence matters in clinical practice and post-marketing drug surveillance. Int J Risk & Safety in Medicine 15, 161-169.

In a proportion of patients who are able to discontinue by taper, ongoing problems in many cases of very significant severity can be expected to continue for months or even longer. In my clinical experience, a proportion of cases, perhaps as high as 5-10%, patients on Paxil will be unable to discontinue by any means.

In the case of patients who cannot discontinue, there are very real problems to be faced. SSRIs emotionally blunt people[9]. If an individual who is unable to stop treatment is one who suffers clear emotional blunting on the drug, such a patient would be therefore condemned to a life in which they will be unable properly to appreciate a range of things from music or other works of art to a range of important emotional experiences.

This can be illustrated by the sexual difficulties such patients face. One of the consequences of Paxil intake that has been linked to its capacity to cause emotional blunting is sexual dysfunction. In both men and women, this drug delays or inhibits the capacity to have an orgasm. Patients unable to discontinue treatment are thereby locked into a permanent sexual dysfunction.

SSRIs have also been associated with a range of problems from brain cell loss in animal models[10] through to gastrointestinal hemorrhage[11], uterine hemorrhage[12], cerebral hemorrhage[13] and cardiac problems in humans.

Aside from the enduring risks ongoing treatment poses, the severity of the anxiety that withdrawal engenders can be extreme. The data from the 30 days post taper phase in Paxil RCTs shown in Tables 4 & 5[14]:

Table 4: Incidence of possibly suicide-related events: all placebo controlled trials 30 days post-taper

	Paxil %	Placebo %	Odds Ratio
Overall	33/9219 0.36%	8/6455 0.124%	2.90
Depression	22/3769 0.584%	3/2402 0.125%	4.67
Non-Depression	11/5450 0.201%	5/4053 0.123%	1.63

Table 5 Incidence of suicide-related & hostility events: all placebo controlled trials 30 days post-taper

	Paxil	Placebo	Odds Ratio

9 For a good account of this see Walsh H (2003). Touching the Void, Guardian Thursday June 12th.

10 Kalia M, O'Callaghan JP, Miller DB, Kramer M (2000). Comparative study of fluoxetine, sibutramine, sertraline and dexfenfluramine on the morphology of serotonergic nerve terminals using serotonin immunohistochemistry. Brain Research 858, 92-105.

11 Oksberg-Dalton S et al (2003). SSRI-Related Increases in GI Bleeding Risk Greatly Potentiated With NSAID Use. Arch Intern Med 163,59-64.

12 Meijer. Archives of Internal Medicine

13 Singhal A et al (2002). Cerebral Vasoconstriction and Stroke After Use of Serotonergic Drugs. Neurology 58, 130.

14 Data from Glaxo SmithKline Archives, and from CSM Expert Working Group on Safety of SSRIs

	%	%	
Overall	43/9219 0.466%	8/6455 0.138%	3.38
Depression	24/3769* 0.637%	3/2402 0.142%	4.45
Non-Depression	19/5450 0.349%	5/4053 0.135%	2.56

* Plus one pediatric hostility event in 30 days post taper.

This is a rate of 3 suicide related or hostility events per thousand. The true figure is likely to be higher as events in the 30 post taper phase were not recorded as well in early trials. It is also the case that events in real life may be quite a bit higher than this as subjects are stopped or stop abruptly from a 20 mg dose or higher, because no-one has warned them about the potentially lethal risks from withdrawal. It is of some interest that these events occur in both depression and non-depression trials and therefore cannot be put down to any one disorder. The data from trials where Paxil is compared to other agents shows that it causes more of a problem than other drugs.

The company response to this clinical problem from 1997 through to 2004 was to campaign aggressively on a number of fronts. These involved claiming any problems were common to all SSRIs, were mild in any event and self-limiting and that the short half life of Paxil provided advantages compared to other drugs like Prozac. The campaign involved rolling out a series of articles by opinion leaders emphasizing that the withdrawal issues were of no concern to clinicians and that it would be a much greater evil to leave patients untreated.

It was not until 2004 GlaxoSmithKline changed their product information under the heading of adverse events from pediatric clinical trials to state that:

In studies that used a tapered withdrawal regimen, symptoms reported during the taper phase or upon discontinuation of paroxetine at a frequency of at least 2% of patients and that occurred at a rate of at least twice that of placebo were: nervousness, dizziness, nausea, emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts, and attempted suicide) and abdominal pain.

This statement is consistent with the data from adult populations and indicative of the severity of the problems. The data make it clear that a statement comparable to this should be present on the labeling for adults also. It should be noted that a great deal of the data underpinning the increased risk of suicidal acts during the withdrawal phase, in table form above, was generated in the 1980s and early 1990s.