Questions to FDA

1/ In the light of Traci Johnson's death on February 7th 2004, will FDA obtain Pfizer's entire folder on the 1982 Hindmarch study in which healthy volunteers were given Zoloft, and make a statement as to whether data of this kind can indicate whether SSRIs can induce suicidality?

2/ Will FDA undertake to obtain all of Glaxo SmithKline's trials in children and make available an analysis of all the data in regard to suicidality and aggressive behavior?

3/ In the light of the details below, will FDA comment on their characterization of the British approach to the question of the risk benefit ratio for SSRIs in pediatric populations as superficial?

4/ Will FDA confirm that companies have inappropriately coded suicidal acts under the heading of placebo in trials of Prozac, Zoloft and Paxil in adults, and will the agency give a true set of figures for the suicidal acts on both active treatment and placebo in registration trials for adults?

5/ Given that Paxil/Seroxat shows the greatest number of withdrawal syndrome reports to WHO for any psychotropic drug ever, and given that the full dimensions of this problem remain unknown, with the company changing its estimates as to the frequency and severity of the problem at regular intervals, will FDA outline exactly how a randomized withdrawal design could demonstrate these drugs work for either children or adults?

6/ Given the abundance of evidence that physicians commonly increase the dose of SSRIs when faced with a patient not doing well on treatment, particularly during the early phases of treatment, what advice will FDA offer to doctors to minimize the risk of this happening inappropriately?

7/ What will FDA do to remedy the incredible fact that Americans track the fate of parcels through the post 100 times more accurately than they track the death of children and adults on these drugs?

8/ Specifically, in the light of the failures of physicians to report adverse events, will FDA consider an initiative begun by the mental health charity, MIND (UK) to foster consumer reporting of drug induced adverse events?

February 19th, 2004

Peter J. Pitts
Associate Commissioner for External Relations
Food and Drug Administration
Parklawn Building
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Rockville MD 20857
United States of America

Dear Mr Pitts

This open letter follows a meeting organized with you by Jennifer Tierney on February 3rd 2004, the day after the PDAC hearing on the use of antidepressants for children. At this meeting, Dr Temple invited a submission of the details of studies referred to in the course of a presentation of the issues. This letter, which will probably be posted on the MIND UK website, linked to Richard Brooks presence at the February 3rd meeting, seeks to do just this.

1/ Healthy volunteers and Non-Depressed Patients

A great number of the patient testimonies in the course of the Feb 2nd hearing were from individuals who became suicidal on an SSRI when their underlying disorder was Lyme Disease, migraine or a condition such as social phobia.

This had also been the case in the 1991 hearings, when it was framed by Dr Temple as follows (transcript page 266):

> "The discussion we heard earlier showed that people who commit suicide are highly likely to have a diagnosis of depression, which means that somebody identified them as in a high-risk category. But there were still a significant number of people who committed suicide without having that sort of diagnosis and I guess I would like some advice or discussion on who those people were.
>
> I ask for the following reason. The anecdotes that one hears that are most evocative to me anyway are not the ones where people who have a 20-year history of suicidal ideation and then finally do it – that is not too surprising – it is where they assert that there has never been anything in their minds like that before and yet now they have suddenly become excessively concerned with suicide and may even do it".

Despite his eloquent statement in 1991, when the question came up on February 2nd and 3rd of the relative contribution of the disease and the treatment, Dr

Temple appeared to be unable to tease out the contributions from these two sources. In the 1991 hearings, he had put it that FDA was faced with a problem comparable to deciding if an anti-angina drug could cause angina.

But in fact the antidepressant field is built on the universal belief that at least one drug with antidepressant properties, reserpine, causes suicide. This belief hinges on the fact that all the recorded suicides on reserpine happened in normal individuals who were taking this drug as an anti-hypertensive. It was in the context of reserpine use that clinicians first began to describe an activation syndrome of the type that the 2004 PDAC pediatric psychopharmacology meeting indicated that FDA should warn parents and doctors about.

In the SSRI trials of healthy volunteers, this issue reaches perhaps its greatest definition. Such phase 1 studies were conducted by companies on their drugs during the 1980s. One of the most illuminating of these studies involving Zoloft was conducted by Hindmarch et al in Britain in 1982.

At a deposition in Miller v Pfizer, counsel for Pfizer, Malcolm Wheeler, said that this study was sent to FDA and other regulators. Mr Wheeler asked whether I had forwarded details of a healthy volunteer study, involving Zoloft, in which two volunteers had become suicidal, that had been undertaken by my group in North Wales to the regulators.

On April 6th 2000, I wrote to MHRA and FDA reporting the data from the North Wales Zoloft healthy volunteer study and asking whether comparable data from any company study had been reported to FDA/MHRA. FDA never acknowledge receipt of my letter (faxed to Dr Laughren).

My correspondence with MHRA is on the socialaudit.org website. In the course of this it became clear that MHRA at least initially did not have access to and had no awareness of the Hindmarch study and its significance. Subsequently the MHRA appeared to have operated on the basis of a four-page summary of the study prepared for them by Pfizer.

Anyone familiar with the conduct of Phase 1 studies will know, particularly when things go wrong, that the paperwork can amount to several hundred pages between the data pages, diaries of healthy volunteers, and reports prepared by company representatives on problems encountered in the course of the trial. If these details were made public in this case I believe that it would be clear that the induction of agitation, or an activation syndrome, that can include suicidality and homicidality was a recognized class effect of SSRI medication in the early 1980s.

It may be that “activation” was rationalized in the 1980s as occurring in “normal brains”, whereas the drugs would ultimately be given to people who were depressed. But the testimony at both the 1991 and 2004 FDA hearings was of

such effects developing in people who were not depressed and SSRIs are now commonly given to people who are minimally, if at all, depressed.

In the course of the February 3rd meeting Dr Temple conceded that it is well recognized that SSRIs can cause agitation, but he then went on to claim that the link between agitation and suicidality had not been demonstrated. DSM-IV however clearly links akathisia to suicide and akathisia in clinical trials of both healthy volunteers and patients is commonly coded under the heading of agitation, when not coded as emotional lability.

From a safety point of view, this issue is more appropriately turned on its head. It is clear that the companies have not attempted to characterize the nature of this agitation, so that for all FDA know every single healthy volunteer who has become agitated on SSRIs may also have become suicidal. These issues have not been explored, or if explored the details have not been recorded. However, in the case of the Hindmarch study, I would think many reviewers accessing the data in its entirety would conclude that the agitation could include suicidality/ aggression.

In addition to Zoloft trials in which there has been a dose dependent induction of agitation in healthy volunteers (Saletu et al 1986), there have for instance been Paxil/Seroxat healthy volunteer trials in which every volunteer dropped out largely for neuropsychiatric reasons. The explanations offered by FDA reviewers for this - namely that these trials were being conducted in medical students who were likely to be more sensitive to treatment side effects than others, or that trials were being conducted by investigators new to the business – might be amusing in another context.

The question of suicide in normals has come to the fore with news that a 19-year old girl, Traci Johnson, in one of Lilly's healthy volunteer trials of duloxetine committed suicide on February 7th 2004. At least one further volunteer in the Paxil/Seroxat program of trials in the 1980s committed suicide. There may have been others. From FDA's point of view are these and all the other testimonies presented at the February 2nd hearings simply anecdotal deaths?

CMAt Document, October 1998:
This document, sent to the BBC following a series of BBC programs on Seroxat/Paxil, was left with FDA on February 3rd (See Appendix 1).

The Central Medical Affairs team (CMAt) was a division within SmithKline Beecham, which helped manage issues across SmithKline's portfolio of drugs, such as withdrawal, weight gain on treatment, or difficulties with sleep etc. The emphasis was generally on either refuting the claims being made by critics or other companies or putting the claims in context – thus all antidepressants cause weight gain or may cause dependence, we're no worse than others etc.

As of 1992, SmithKline and other companies were asked by FDA, as part of the approval process of their drug for adults, to conduct studies of their drugs on children, as these drugs would be used off-label and it was therefore important to know whether there were any safety issues.

CMAt were faced with the results of a trial, Protocol 329, which was run from 1993 through to late 95/early 96. This was the biggest, and best trial of any SSRI undertaken in children. Its results were conclusive. Seroxat/Paxil in general didn't work. The results in terms of hazards were also conclusive; Seroxat/Paxil had a statistically significant excess of suicidal acts compared to comparators – 5 suicidal acts from 93 children on Seroxat/Paxil compared to none from 89 children on placebo and 1 from 184 children on either imipramine or placebo. Furthermore roughly 10% of the children had psychiatric side effects on Seroxat/Paxil, which is particularly significant against a background of failure to demonstrate that the drug worked.

These results from Protocol 329 gave rise to the dilemmas CMAt deal with in this document. One option was to publish only the positive results from the study. The study was in fact published in 2001 – 5 years later – as Keller MD, Ryan ND, Strober M, Klein RG, Kutcher SP, Birmaher B, Emslie G, Wagner K et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry 2001 40: 762-772. The authorship line of this paper included many of the most distinguished figures in US psychiatry. The paper concluded that Paxil/Seroxat given to children was safe, effective and well-tolerated.

In the published version of 329, suicidality vanishes under a carpet of emotional lability. While this is a legitimate side effect coding term, few readers of this paper, academic or lay, will have realized what lay behind this term as it appeared in the paper. Similarly in this and other Seroxat/Paxil pediatric studies aggressive events disappear under the heading of hostility, a term that covers homicidal acts, homicidal ideation and aggressive events.

CMAt's recommendation was not to send the data to the regulators, as FDA will have to advise that the label state that Paxil/Seroxat in trials has not been shown to work for minors, as not including this would encourage off-label use.

The issue of suicidality was not raised in the document, perhaps because SmithKline was confident it could conceal this problem under terms like emotional lability – see below.

At that point in time the overwhelming commercial imperative for SmithKline referred to in this document may well have been their adult market. In the UK there were at this stage roughly 500,000 adults on the drug each year and perhaps 8-10,000 children/teenagers. In sales terms children were insignificant.

In the US, at this time there were c 3 million people annually starting Paxil, with a further 3 million taking it chronically – see below. Something like 100,000 children started treatment annually on Zoloft and on Prozac and on Paxil/Seroxat – a relatively small proportion of the total. The number of children may have been growing fast however, following front page promotions of teenage depression in Newsweek in 2002, and the publication of the Keller et al (329) article in 2001, which had a considerable impact on clinicians. Work by Zito and others suggests that a significant proportion of this childhood group in both the US and the UK were preschoolers, in some cases as young as 1 year old.

The CMAt document makes it clear that another protocol, 377, was even more comprehensively negative than 329. There were no plans to publish 377. Dr Laughren's presentation at the PDAC hearing referred to some children having more than one suicidal act; was that a problem affecting this protocol? There must also be a concern in a protocol conducted in South American and South Africa back in the mid-1990s that a number of children may have been lost to follow-up making the issue of whether they actually committed suicide or not unknowable; did this affect this protocol?

The company has not revealed any details about study 511 cited in the CMAt document or study 716, and it appears from statements by Drs Temple and Katz immediately after the Feb 2nd meeting that FDA have not seen either of these studies

The Post CMAt Evolution of Events

As put forward by the FDA at the PDAC hearings on February 2nd, the data on suicidal acts in these Glaxo SmithKline trials became clearer following a request by FDA to the company to clarify the events that lay behind the term emotional lability. This was in October 2002.

At the same time, study 329 featured in the first Panorama program on Paxil/Seroxat. The Panorama programs intersected with Glaxo-SmithKline's later application to the MHRA to seek a license for Paxil/Seroxat for minors for social phobia and OCD in the UK. This application, as I understand it, led MHRA to request the data from Glaxo SmithKline's trials in pediatric depression. This data came in a form that clarified what emotional lability meant, leading MHRA to issue a first warning. FDA apparently had not received the data at that point, over 6 months after asking for it.

However, an even fuller sequence of events is that FDA officials, S Galson and J Alexrod, met with Messrs Faber and Murgatroyd in early October 2002, who suggested that FDA should investigate Glaxo SmithKline's use of the term emotional lability in their clinical trial programs. Emotional lability has been listed as a "frequent" adverse event for Paxil/Seroxat ever since the original label for the drug was approved in late 1992. It was only after this meeting that FDA asked the company to clarify the meaning of the term emotional lability.

An Analysis of Suicidality in SSRI Pediatric Trials

This sequence of events led me, when visiting Glaxo-SmithKline's archives in Philadelphia in the course of In Re Paxil litigation, to look at indices of withdrawal from Paxil/Seroxat trials in children, as a warning letter to doctors in the UK from GSK in June 2003 had indicated that during the withdrawal phase of treatment children were at increased risk of becoming suicidal.

I reviewed protocols 329, 377, 701, 453, 658, 704, on which FDA have based their assessments of this drug, as well as protocols 715 and 716, assessing among other things the narrative summaries on all patients where these were present as well as details of adverse events such as investigator's judgments as to the relatedness of these events to drug intake and the relationship between the time of any dose change and the adverse event.

On the basis of this review, as well as comparable reviews of other data from adult trials, and combined with statements in the published literature, it is possible to make the following points about the data sent to FDA. These points, I believe, justify the approach taken by MHRA towards the data, namely that it is not worth worrying too much about getting the "signal" from these trials fixed as accurately as possible as the methodologies are so poor that retrospective tinkering of the type currently proposed by FDA does not seem warranted.

First, the narrative summaries that FDA propose to send to the Columbia psychiatric group for blind review of suicidal content are not blindly constructed. In these trials, there would appear to be a systematic bias on the part of the clinical investigators to deny the role of active drug in the causation of problems; which may in fact be supplemented by a tendency to blame placebo for problems with suicidality where these occur in association with each other. Against this background, the non-blind construction of these summaries along with the many psychosocial events that narrative summaries in this domain typically include will commonly give enough doubt to enable a re-categorization of suicidal acts to suicidal gestures or other categorizations.

Second, narrative summaries in general are typically only present for the final suicidal episode or adverse event that leads to discontinuation from a study, but in SSRI trials some children have had more than one suicidal episode. Against a background of investigator reluctance to credit suicidality to the active drug, it is highly likely that the majority of unrecorded suicidal episodes/acts will have occurred in the active treatment group rather than on placebo. In other words, the true picture as regards the number of suicidal acts may be considerably worse than is currently represented in the data.

Third, FDA appear to have ignored the issue of any relationship between dose change and suicidal events, even though the letter from Glaxo SmithKline to

healthcare professionals in the UK now states clearly that dose lowering of Paxil/Seroxat may lead to suicidality.

Fourth, it seems clear from conversations with Drs. Temple and Katz that there is data FDA have not seen Glaxo SmithKline's protocols 511 and 716, for instance. These can be expected to yield a further number of narrative summaries, as can other studies such as 715.

Finally, many observers with clinical trial experience will guess that it is highly likely that a number of children who dropped out of these pediatric studies which were organized in South America, South Africa and elsewhere will have been lost to follow-up, so that FDA statements that no children enrolled in these trials committed suicide may well be in error.

I have analyzed the data from pediatric trials for suicidality and hostility using Paxil/Seroxat protocols 329, 377, 453, 676, 701, 704 and 716, supplemented by data from GSK's Canadian website, FDA medical reviews of Prozac trials for depression and OCD, published data on Zoloft/Lustral as well as an expert report prepared for Pfizer in 1997, and one of two studies on Cipramil taken from the MHRA website. A second study gives a more favorable picture for Cipramil, but I did not become aware of this study until after the analysis was finished. The results from that study would not substantially affect the results outlined here.

This analysis does not include data on venlafaxine, mirtazapine, nefazodone or buproprion. Wyeth has independently indicated that venlafaxine should not be used in children because it causes suicidality and hostility. Nefazodone has been removed for adults from European, Canadian and Australian markets.

I have broken down the studies into a group of depressed and a group of anxious studies, which involve children being treated for obsessive-compulsive disorder (OCD) or social phobia. Because I am subject to confidentiality orders, the data cannot be broken down by individual trials.

From a pool of 931 depressed patients taking the above SSRIs versus 811 depressed patients taking placebo, there were 52 suicidal acts on SSRI versus 18 on placebo. This is a 5.6% rate versus a 2.2% rate or a relative risk of 2.51. The data was analysed using a Mantel Haenszel procedure. The default procedure here gives a point estimate of the common odds ratio of 2.51, (95% C.I., 1.46, 4.34, $p = 0.000899$).

In a pool of 638 anxious patients taking SSRIs versus 562 anxious patients taking placebo, there were 10 suicidal acts in the SSRI group versus 1 in the placebo group, a 1.6% rate versus a 0.18% rate. When the data was analysed using a Mantel Haenszel procedure, the point estimate for the common odds ratio 11.31 (95% C.I. 1.34, 95.64, $p = 0.0156$).

This data is consistent with independent contributions from both the illness and the treatment. Depression carries with it a greater risk of suicidal acts than do the anxiety disorders, but in the case of the anxiety disorders the risk from treatment is no less than in the case of depression.

When these data sets are combined in 1569 patients put on SSRIs there were 62 episodes of suicidality versus 19 episodes in 1373 patients put on placebo. This is a 4% rate in the SSRI group versus a 1.4% rate in the placebo group, or a relative risk of 2.9 times greater on SSRIs. Using a Mantel-Haenszel procedure, the point estimate for the common odds ratio is 2.91 (95% C.I. 1.73, 4.91, p = 0.000041). These figures parallel the figures from adult trials submitted to the FDA as part of the license applications for recent antidepressants.

In analyzing the adult data, I started from FDA medical reviews of recently licensed antidepressants for adults. The critical methodological point in these adult studies is that it is now apparent that Lilly when submitting their data on Prozac to FDA filed as placebo suicides and suicidal acts, acts that had not happened on placebo, but had happened during the run-in phase of the trial, or that had happened months after the clinical trial was over (See Appendix 2). Despite FDA recognition that these procedures are inappropriate, Glaxo SmithKline and Pfizer have also filed under the heading of placebo suicidal acts that did not happen in the randomized phase of their respective trials (See Appendices 3 & 4).

Once this is taken into account and the figures adjusted accordingly (see Table 1), the results for SSRIs versus placebo using an exact Mantel-Haenszel procedure, with a one-tailed test for significance, the odds ratio of a suicide on these new antidepressants as a group compared to placebo is 4.40 (95% Confidence Interval is 1.32 – infinity; p = 0.0125). The odds ratio for a suicidal act on these antidepressants compared to placebo is 2.39 (95% Confidence Interval 1.655 – infinity; $p \leq 0.0001$). The odds ratio for a completed suicide on an SSRI antidepressant (including venlafaxine) compared to placebo is 2.46 (95% Confidence Interval 0.707 – infinity; p = 0.16), with an odds ratio for a suicidal act on SSRIs compared to placebo of 2.22 (95% Confidence Interval 1.47 – infinity; $p \leq 0.001$). These data have been the subject of two peer review publications at this point.

There is a striking overlap between the results in trials from adults and pediatric trials. While the rate of suicidal acts is higher in pediatric trials of depression, the relationship between active treatment and placebo is the same in both adult and pediatric groups. It should also be noted that the suicidality issue in these pediatric studies is not a matter affecting the 6-12 year old age group, showing a decline thereafter through the teenage years that could be extrapolated into adulthood. On the contrary, as Glaxo SmithKline make clear, the issue affects teenagers much more than preteens.

Finally, Glaxo SmithKline's website also contains data on acts of hostility from 4 different protocols. I have been able to review the narrative summaries and data from these and one further protocol. These protocols combined yield a total of 524 patients on Paxil/Seroxat versus 526 on plabebo, with 31 hostile episodes on Paxil/Seroxat versus 2 on placebo. Using a Fisher exact test for count data, this gives a point estimate of the common odds ratio of 15.54 (95% C.I. 3.92, 134.91, p = 0.000001).

These results are in line with the analyses of the data conducted by Andrew Mosholder of the FDA and by the MHRA, but excludes a number of drugs these authors included. This analysis represents a much purer set of SSRI drugs, and more data on SSRI drugs than has been available to other reviewers.

Crisis in the scientific literature

One of the key points about this issue is the crisis it points to in the scientific literature. All of the articles on randomized trials on Prozac, Zoloft, Paxil/Seroxat and Efexor, whether in full publication or in abstract form, describes these drugs universally as safe, effective and well-tolerated. This is despite the fact that it is now clear that in the opinion of FDA, and MHRA reviewers and others that in 13 or 15 depression trials the drugs were not effective, and not safe.

Furthermore it is clear that in many instances these drugs may not be well-tolerated in that 10% of children have psychiatric side-effects on Paxil/Seroxat, in study 329, and in the combined Zoloft depression trials 9% of children drop out for adverse events. In other Zoloft trials (Alderman et al) the rate of suicidality on the Zoloft was 9% in depressed children. The published article on this latter study reports on adverse events that occurred at a 10% rate or more and hence it fails to mention that there was any issue with suicidality in these children. A further article on Zoloft by Ambrosini et al, which reports on a 5.7% rate of suicidality on Zoloft, says that "Sertraline is effective, safe and well-tolerated".

There is probably no other area of medicine in which the academic literature is so at odds with the raw data. A possible explanation is that this literature has had a significant ghostwriting input, a possibility that the ACNP Task Force Report, published 10 days before the FDA hearing and widely seen as a pre-emptive strike at FDA, does nothing to dispel. The Task Force reported SSRIs to be effective, safe and well-tolerated, but the authors claimed that they might be mistaken in that they had not seen the raw data. The authors of the Task Force Report, however, include Emslie, Wagner and Ryan who are authors on almost all of the randomized trials on SSRIs, in addition to study 329. On what basis can they claim not to have seen the raw data?

Symbolically perhaps, the ACNP Report states it had medical writing input and for a considerable period of time following publication, this report was not available from ACNP offices. Those who wished to get the document were referred to GYMR, a public relations company in Washington, whose medical

writers "know how to take the language of science and medicine and transform it into the more understandable language of health".

The CMAt document shows what may be involved. The authors of this document state that "positive data from study 329 will be published in abstract form and a full manuscript will be progressed". Science depends on access to, or a fair representation of, all of the data. Portraying positive only results as science, in other settings, has been called fraud.

While it is not FDA's brief to regulate the academic literature, the possibilities of a close to fraudulent representation of data and of extensive ghostwriting does set up an argument that these apparently scientific articles are in fact infomercials rather than the real thing. If these articles are essentially advertisements, it is much less clear that FDA can throw their hands up and plead an inability to do anything about the production of such materials, when such materials have almost certainly in the case of study 329 led to a significant increase in off-label use of Seroxat/Paxil, while the company behind this article stalled on handing over data to FDA that had been generated in the first instance following an FDA request to have such data for safety purposes.

This is a matter with financial as well as safety implications. Emslie and Wagner are also authors on the Texas Medication Algorithm Project (TMAP), recently reported on in detail in the New York Times. The TMAP guidelines regarding the treatment of children endorse the use of SSRIs as safe, effective and well tolerated. In this case, this guideline leads directly following legislative recommendation to children in public care being given SSRIs over any other treatment that may be appropriate, at clear risk it would seem to these children and a clear cost to the public purse. These guidelines have been adopted by a number of states including Pennsylvania, California, Colorado, Nevada, Illinois, Kentucky, New Mexico, New York, Ohio, South Carolina, Maryland, Missouri, and Washington D.C., so that a very large number of children and medication dollars are involved.

The Adult Market

CMAt's target was "to effectively manage the dissemination of these data in order to minimize any potential negative commercial impact." The most reasonable guess as to what this means would seem to be that GSK were concerned about the effect any perception of lack of efficacy might have for sales in their far more lucrative adult market.

This raises the question of how many people have been taking Prozac, Paxil and Zoloft since launch. One of the extraordinary features of the current crisis is that neither FDA nor the pharmaceutical companies, nor regulators elsewhere know how many people in the USA, the UK or elsewhere have had Prozac, Paxil/Seroxat or Zoloft since they were launched. No-one knows how many people are on these drugs for 1, 3 or 5 years or more.

The question of how long patients may be taking these drugs needs to be interpreted against a background of the best epidemiological evidence indicating that depressive disorders last on average for 12 to 16 weeks. While some patients taking these drugs for longer may be taking them for prevention purposes, a further possibility has to be that a significant number of people are now physically dependent on treatment.

The number of patients is important for a further reason, which is that if there is a risk factor from suicide on these drugs then the numbers of people who have taken the drugs will determine the number of people who may ultimately have suffered from treatment.

In October 2001, Graham Aldred's wife, Rhona, was anxious and was prescribed Paxil/Seroxat by her GP. In the following week Rhona Aldred suffered a progression of mental side effects from this drug of increasing severity, which retrospectively appear to be the classic features of SSRI induced agitation. Her husband, assuming that her doctor would have done the best for her, and in the absence of any warnings, encouraged her to persevere with the treatment. On the 11th day of treatment, November 8th 2001, she committed suicide. This was a woman with no prior history of nervous problems. Her medical records at the inquest did not record either her death or any link between her death and SSRI intake.

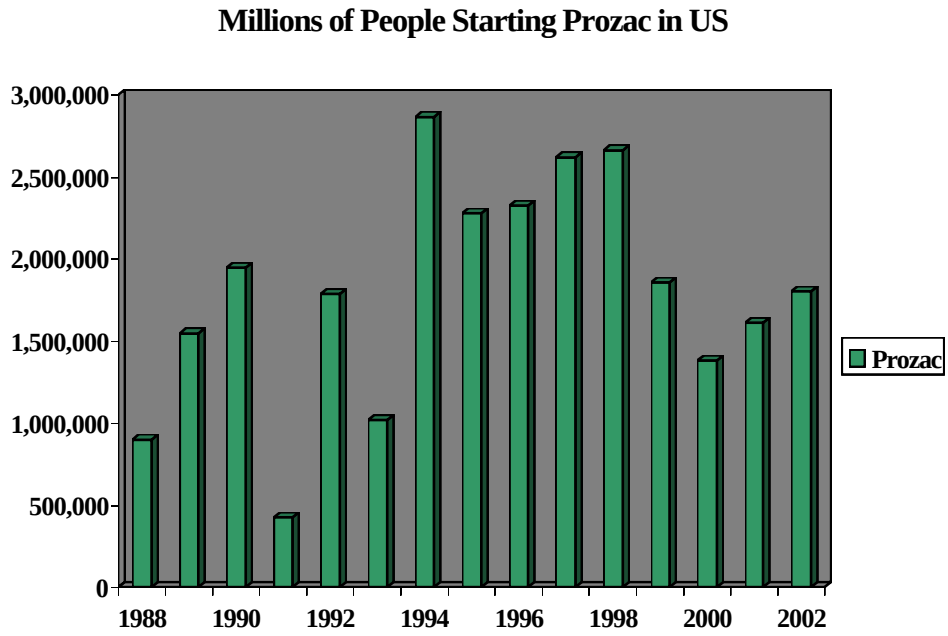
Her husband later became aware that the extent of the problems being caused by these drugs could not be quantified as no-one in the UK knew how many people had been taking Seroxat/Paxil or any other SSRI. Graham Aldred's background in systems engineering, logic design and diagnostic analysis, led him to produce a model (IMR – see Appendix 5), which gives the best figures available for how many people have been taking SSRIs in the US and the UK.

Data for this purpose came from three places. First, data from the Department of Health in the UK as to the physical amounts and numbers of prescriptions of Prozac, Seroxat/Paxil and Lustral/Zoloft since their launch in 1989, 1991 and 1992 respectively. Second, data for the US came from IMS Health.

A third data source was from the Drug Safety Research Unit (DSRU) in Southampton, a prescription event monitoring service. DSRU tracks the effects of drugs new to the market during the early months of a drug's life. In the case of the SSRI drugs, this exercise was carried out for Prozac, Faverin/Luvox, Paxil/Seroxat, Lustral/Zoloft, giving a total of 50,540 patients, whose profiles illustrate how many patients typically drop out of treatment after a one, two, three, four, five or six months etc. DSRU studies also give the number of deaths, including deaths by suicide. This profile is confirmed by a good deal of other research in the field.

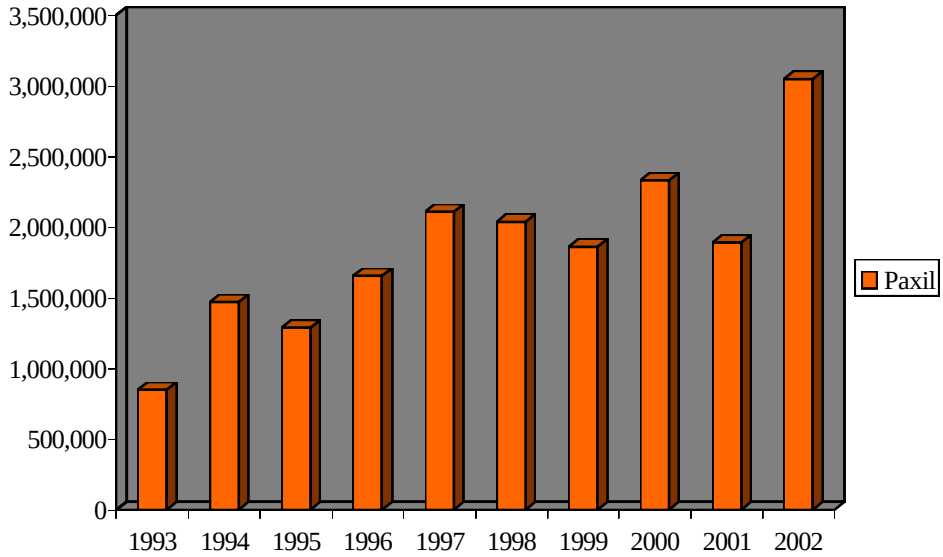
Using this profile of drop out from treatment, it becomes possible to convert the amount of drugs sold and number of prescriptions issued into the numbers of people actually taking a drug or starting a drug in any one year.

This leads to the following annual figures for millions of Americans taking Prozac (Figure 1). If we extrapolate to 2003, over 28 million people have started Prozac since its launch in 1988.



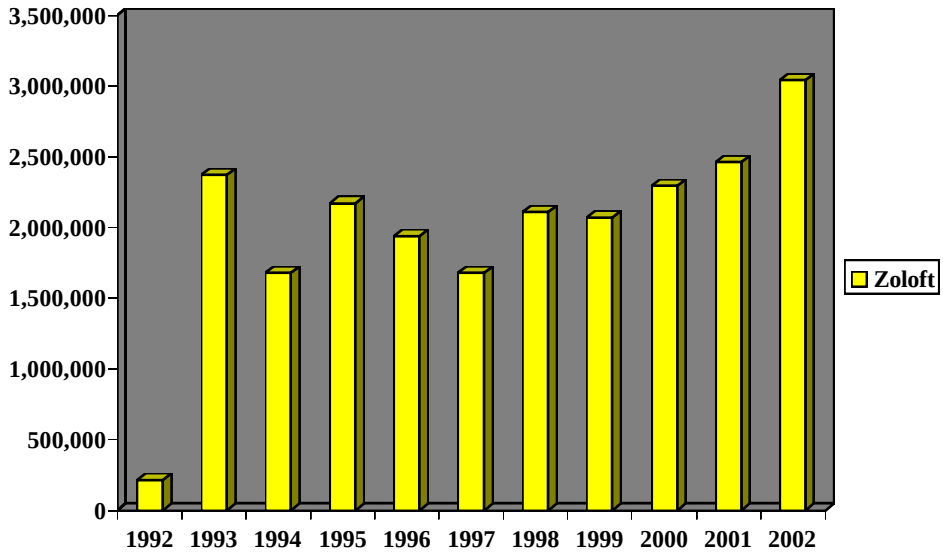
The annual figures for Paxil extrapolated to 2003 (Figure 2) show over 21 million Americans have started Paxil since its launch in 1992.

Millions of People Starting Paxil in US



The annual figures for Zoloft extrapolated to 2003 (Figure 3) show over 24 million Americans have started Zoloft this since its launch in 1992.

Millions of People Starting Zoloft in US

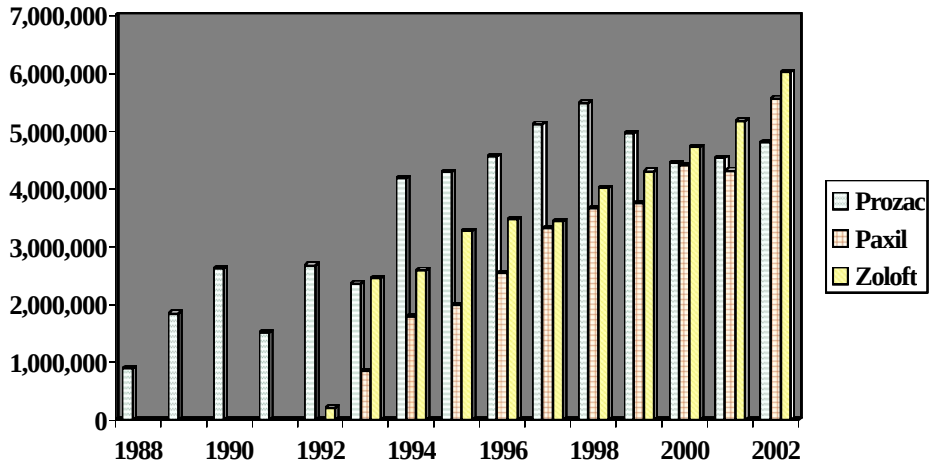


In total, there have been over 75 million treatment starts on Prozac, Paxil/Seroxat and Zoloft since these drugs launched in the US. Taking into account the fact that some patients will have had two or three of these three drugs, or one of these drugs on more than one occasion, a reasonable estimate of the numbers of patients exposed to one of these three major SSRIs may be as high as 50

million Americans. To this must be added figures for the numbers of people who have independently taken the SSRIs Celexa, Efexor, and Lexapro, as well as Serzone, Remeron and Wellbutrin.

The IMR model also gives figures for the numbers of people taking these drugs for a year or more. Figure 4 indicates that there are over 16 million Americans taking Paxil, Prozac or Zoloft at some point during 2002. This suggests up to 30 million American may have an antidepressant in any one year. And in fact we appear to have reached a point where more than half of those taking Paxil, Prozac or Zoloft are on these drugs for more than a year.

Overall Annual Usage of SSRIs in USA



Of these patients, the numbers of people now taking Paxil, Prozac and Zoloft in the United States for one year or more is 8.3 million, the numbers taking these drugs for three years or more is 5.6 million, the numbers taking these drugs for five years or more is 3.8 million.

The Number of Excess American Suicides

From these figures, it is also possible to derive estimates of the numbers of excess deaths there have been on Prozac, Paxil and Zoloft. Clearly there must be an excess of risk for there to be any excess suicides. But even on the most favorable analysis for the FDA, that undertaken by Kahn et al in 2000, there was an excess of suicide and suicidal acts on active treatment compared to placebo, confirmed by in a subsequent publication by Laughren. This did not reach statistical significance but the best possible estimate remains one that exceeds the rate for placebo.

Many people believe that antidepressant treatment when successful can reduce the risk of suicide and there is evidence that patients who are suicidal in the

course of a response to treatment become less suicidal. If this is the case, the excess of suicides found by Kahn et al would then in fact represent an even greater excess if selected from among those patients who do not show suicide risk reduction.

The FDA at present says that it is undertaking a re-analysis of its database on the lines of that undertaken by Khan and colleagues, and that the new approach will pick up some of the issues that have arisen regarding the matter. This is not likely to restore confidence in the market unless it comes with explicit reassurances that FDA has excluded from the heading of placebo any suicidal acts that had occurred during the run-in phase of clinical trials or during the phase after the formal trial had ended. It would seem likely that the true figures for suicidal acts in trials of other antidepressants currently on the market such as Celexa, and Efexor would show fewer placebo related suicide events than the current trial literature suggests (See Table 1). Perhaps FDA could clarify this.

Re-analyzing the Kahn data as outlined above it is clear that there have been approximately 180 suicides per 100,000 exposures to antidepressants compared with a figure of 68 per 100,000 exposures to placebo – an excess of 100 per 100,000 exposures to active treatment.

The DSRU figures give 212 suicides per 100,000 exposures to SSRIs. This figure drawn from UK general practice can best be compared with the Jick et al 1995 figures, derived from approximately 200,000 patients in UK general practice, who in almost all instances had treatments antedating the SSRIs, which gave figures of 68 per 100,000 patients. Comparisons of these two data sets again suggests that SSRI treatment is associated with 100 suicides per 100,000 patients in excess of the rate that would have otherwise existed on treatment with other drugs or non treatment. Despite requests for other input data from MHRA and others, no other group has offered us any other input data to the model than this.

In order to estimate the number of suicides that have actually happened in the US however it must be recognized that the patients initially given SSRIs in the US/UK may have been depressed and at greater risk of suicide than those patients subsequently given SSRIs in both the US and the UK, of whom an increasing proportion will have been either less severely depressed or anxious patients or indeed patients given these drugs for weight loss, migraine or other purposes where the risk of suicide was effectively either that of the normal population or even lower. To account for this problem we have constructed a grid, which assumes a rate of 100 suicides per 100,000 patients if all patients entered into this study were relatively severely depressed, or a rate as low as 32/100,000 suicides if all patients were anxious. The matrix then includes estimates for the number of suicides if 80%, 60%, 40%, 20%, or 0% per cent of the patients are depressed, and the remainder are anxious.

The resulting estimates for the number of excess American suicides on Paxil/Seroxat, Prozac and Zoloft can be found in Figure 6. For the 100% depression figure, this gives 70,290 suicides, or 90 per week, or 4,686 per year. For the 80% depressed cohort, the figures come to 60,619, 77 per week or 4,041 per year. For the 60% depressed cohort the figures come to 50,939 or 65 per week or 2,396 per year. For the 40% depressed cohort the figures come to 41,260 or 53 per week or 2,750 per year. For the 20% depressed cohort the figures come to 31,579 or 40 per week or 2,105 per year. For the 0% depressed cohort the figures come to 21,900 or 28 per week or 1,460 per year. These gross estimates represent figures averaged over the 15-year period from Prozac's launch in 1988.

The increasing proportion of anxious patients, and US fashions for co-prescribing other drugs, in particular the benzodiazepines, may have minimized some of the risk. However it can be noted that the model discounts all those suicides caused by drug that have been balanced out by patients made less suicidal by treatment. Given these factors, we suggest using our baseline estimate – that is 21,900.

This figure of 21,900 is quite consistent with US suicide rates as they have tracked over the past 15 years. The greatest driver of suicide rates is employment or unemployment and the 1990s have been a favorable time in the United States for employment. It is notable that in some countries where suicide rates had previously been falling such as the United States, Sweden, Finland and Holland, these countries have all posted slightly higher suicide rates this year. Another factor is ethnic mix. Reported suicide is linked primarily to white males. In so far as the ethnic composition of the United States has changed during the course of the 1990s this would lead to a downward fall in national suicide rates whether or not there were treatments for depression.

It should also be noted that as of 1999 the FDA website included details of 2,000 actual suicides that had happened on Prozac many of which were linked to descriptors such as akathisia, so these figures have a basis in dead people. The FDA website for adverse events stresses that at best adverse events if they are serious are reported at a 1 in 10 frequency and that adverse events in general are reported at a 1 in 100 frequency. There is some reason to believe that an adverse event such as suicide would be reported less frequently than other adverse events as it can be seen as a failure on the part of the clinician in the way for example that liver failure may not be construed.

As regards children, Thomas Moore in a presentation to the February 2nd PDAC committee reported the results of a study looking at the proportion of scripts issued for Prozac, Paxil and Zoloft to minors. His figures point to a 5% rate of scripts being issued to children. If 8 million adults had these drugs in 2002, this would yield a figure of 400,000 children or roughly 100,000 per drug. Over the 5 years since the CMAt document, this might have led to as many as 1.5 million children receiving Prozac, Paxil and Zoloft (with even more children on other

agents). An excess suicide rate of 100 per 100,000 would lead to 1,500 excess suicides. The true figure may lie anywhere between 100 to 500 excess suicides for this 5 year period alone and for these 3 drugs alone, with an indeterminate further number of homicidal or seriously aggressive acts. The February 2nd PDAC meeting heard from a large number of bereaved parents or convicted children who appeared to be minimally if at all depressed and who appeared to have a typical signature to their tragedy of drug induced activation.

Withdrawal Designs

The PDAC hearings on February 2nd ended on what for me at least was a surreal note. Given that Paxil/Seroxat shows the greatest number of withdrawal syndrome reports to WHO for any psychotropic drug ever, and given that the full dimensions of this problem remain unknown, with the company changing its estimates as to the frequency and severity of the problem at regular intervals, it is not clear to me exactly how in a pediatric or adult population a randomized withdrawal design could demonstrate these drugs work for either children or adults.

The notion of demonstrating efficacy by a randomized withdrawal design arose in part in the antipsychotic realm before the work of Gilbert, Jeste and colleagues and Baldessarini and others showed that there was a withdrawal syndrome from antipsychotics. In the antidepressant realm, such designs are most closely linked with the work of Stuart Montgomery, and company employees. Studies of this sort, when the company has already conducted studies in healthy volunteers, showing that they become depressed and anxious following relatively brief exposure to treatment would seem deeply cynical. The notion of conducting such studies arose before Lilly began to market the occurrence of withdrawal from Paxil and Zoloft in 1997. Since then no attempt to justify such a design has been made that takes into account changed company positions on the occurrence of “symptoms on stopping” as Glaxo SmithKline now apparently refer to the phenomenon.

Warnings

At the end of the February 2nd hearings, Dr Katz said the FDA had heard a very clear message, phrased by the committee chairman M Rudorfer in terms of a need to put a speed bump on the road of treatment by inserting a warning in the material sent to both physicians and parents. Immediately after the meeting, and the following day, FDA officials talked about strengthening the warnings referring to the early phase of treatment where supposedly everyone agrees there is some risk linked to the illness.

The notion that there is a risk period has only been outlined in the case of mood disorders, it has never been suggested for anxiety disorders and certainly not for Lyme disease, migraine and the other cases FDA were presented with.

FDA officials on both February 2nd and 3rd appeared anxious to avoid committing to any distinction between the effects of the drug and of the illness.

But there is a key question they have been asked and at present have left unanswered. Should the patient whose dose is being increased after several weeks or months on treatment be regarded as a new patient?

The healthy volunteer literature points to a clear dose dependent increase in agitation in healthy volunteers. The literature in depressed or other patients on activation problems arising with SSRIs points to problems in patients arising for instance on a 40 mg dose of Prozac that had not been present on the 20mg dose. Furthermore letters from Glaxo SmithKline to healthcare professionals in the UK now make it clear that suicidality may occur in relation to dose transitions.

There are two linked safety issues here. Physicians who are concerned about the initial phase of treatment but who have not fully grasped the possible contribution of treatment to any problems arising in this phase, when presented with patients having difficulties during this period as a matter of fact are telling their patients to double the dose of treatment. Patient reports on the adverse events that have occurred to them illustrate this clearly – see below. This is exactly the wrong thing to do in cases in which a drug induced activation syndrome is a component of the problem.

Furthermore, while FDA and others may regard a failed suicidal act followed by treatment discontinuation as a near miss, in fact a great number of patients who have had difficulties on SSRIs blame themselves for what happened. In the absence of an authoritative source making it clear that some cases may stem from a drug induced disturbance, many of these affected individuals will have a longer term injury to their self-image, which given that suicidal acts are predictive of future suicides may contribute to completed suicides in the future. Can FDA really do nothing to make it more likely that some individuals at least will have these more subtle injuries addressed?

At the 1991 PDAC hearings on Prozac, FDA bemoaned the poor quality of the trials undertaken that made it impossible supposedly to arrive at a conclusive verdict on the issues. Again in 2004, FDA bemoaned the quality of the trials undertaken and the difficulties in detecting a clear signal from these studies that were not designed to investigate the issues, but added that further clarity was unlikely as these drugs were about to come off patent.

The justification offered by Dr Temple on February 3rd in not seeking any improvement in trial quality after 1991 was that the 1991 PDAC meeting had decided that Prozac was not to blame. This seems odd given that FDA complained in 1991 that the trial data was of such poor quality, and against the background of FDA's own recognition in 1991 of a risk during the early phase of treatment (the rollback risk), and given that FDA had spent a year working with

Lilly on a trial protocol and suicidal ideation scale designed to improve signal quality. This suicidal ideation scale could readily have been put into every subsequent antidepressant trial and could have been part of all the pediatric studies

Consumers

The bottom line to the picture outlined above is that Americans track the fate of parcels put in the post 100 times more accurately than the fate of children or adults dying of these drugs. The answer to this problem is not necessarily more regulation of companies. A system of notification so that all drug intake in the case of a death by suicide must be notified to a central source by the prescribing doctor or by coroners at inquests would make a big difference. This should extend to all drug intake, in that it is now clear that for example bladder stabilizers such as duloxetine may trigger a problem.

Another approach would be to involve those who actually consume the medication given that the proxy consumers, the prescribers, have failed so lamentably in this area. A recent paper in International Journal of Risk & Safety in Medicine 16 (2003) 5-19, by Charles Medawar and Andrew Herxheimer points a way forward here. (See also Herxheimer and Mintzes, Canadian Medical Association Journal 2004, pages 487-88).

This report was the first published critical appraisal of the role of spontaneous adverse drug reaction (ADR) reports in monitoring the safety of marketed medicines using the British Yellow Card scheme which is regarded "as the cornerstone of the Agency's work on medicines safety monitoring", and generally regarded as the best of its kind in the world. The report was also a first review of anonymized Yellow Card reports of suspected adverse drug reactions to Paxil, relating to withdrawal reactions/dependence and suicidal behavior. Finally the report compared the value of ADR reports from drug users and health professionals.

The results pointed to miscoding and flawed analyses of Yellow Cards that have led to an under-estimation of the risk of suicidal behavior, that physician completed adverse event reports typically lack important information (e.g. patient history, dosage; outcome of reaction), and that poor reporting and data processing by physicians have impeded recognition of what appears to be a close relationship between suicidal behavior and changes in drug concentration.

Nevertheless, a reanalysis of the data pointed to an increased risk of suicidal behavior during the first few days of treatment with an SSRI that has long been suspected, even though ADR reports sent in by drug manufacturers systematically obscure this risk by using euphemisms in describing ADRs (e.g. 'Non-accidental overdose' to describe suicide attempts).

In contrast, and of perhaps greatest importance, an analysis of a comparable set of patients reports suggested that these communicate essential information which professional reporters can never be expected to provide, and that these pick up relations of adverse events to dose transition on treatment that professionals miss that have since been confirmed by company statements and an independent analysis of clinical trial data on these drugs submitted to FDA 12 years ago or more as part of the registration process for these drugs. Given the consonance between consumer reports and the clinical trial evidence on matters as serious as this, and given a failure of reporting that would not be tolerable in any other market, there are clearly grounds to think FDA should do more to encourage reporting of this kind.

The points outlined above are summarized in the set of questions, appended to the start of the document. I would be happy to contribute further on issues that the document throws up if this seems helpful.

Yours sincerely

David Healy MD FRCPsych

Table 1: Incidence of Suicides and Suicidal Acts in Antidepressant Trials
See Healy & Whitaker 2003

Investigational Drug	Patient No	Suicide No	Suicidal Act No	Suicides & Acts as a % of Patient No
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%
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 New 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 Placebo	3,140	2	16	0.57%

Healy D, Whitaker CJ (2003). Antidepressants and suicide; Risk-Benefit Conundrums. J Psychiatry & Neuroscience 28 (5) 331-339, with response by Y Lapierre 340-349.

Appendix 1

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October 1998

SEROXAT/PAXIL
ADOLESCENT DEPRESSION
Position piece on the phase III clinical studies

EXECUTIVE SUMMARY

Results from the 2 placebo-controlled, phase III clinical trials designed to assess the efficacy and safety of Seroxat/Paxil in adolescents with major depression are now available.

Study 329 (conducted in the US) showed trends in efficacy in favour of Seroxat/Paxil across all indices of depression. However, the study failed to demonstrate a statistically significant difference from placebo on the primary efficacy measures. The second study (study 377), which was conducted in Europe, South America, South Africa and the United Arab Emirates, showed a high placebo response rate and failed demonstrate any separation of Seroxat/Paxil from placebo.

Data from these 2 studies are insufficiently robust to support a label change and will therefore not be submitted to the regulatory authorities. Results from Study 329 will be presented in abstract form at the ECNP meeting (Paris, November 1999) and a full manuscript will be progressed. There are no plans to publish data from Study 377.

October 1998

SEROXAT/PAXIL
ADOLESCENT DEPRESSION
Position piece on the phase III clinical studies
FOR INTERNAL USE ONLY

SITUATION

2 SB sponsored, placebo-controlled, phase III clinical trials have been conducted, Study 329 (US) and Study 377 (Europe, South America, South Africa and Saudi Arabia), in order to assess the efficacy and safety of Seroxat/Paxil (up to 40mg/day) in the treatment of adolescents (aged between 13 and 18 years and 11 months) with unipolar major depressive disorder (diagnosed according to DSM IIIR, Study 329 or DSM IV criteria, Study 377).

Study 329 was a placebo-controlled, imipramine comparator study with an 8 week acute treatment phase followed by a 6 month extension phase. The acute phase has completed and the extension phase is due to complete at the end of 1998. 275 patients were recruited to the study. Results from the acute phase of this study show that there were no statistically significant differences from placebo on either of the primary efficacy parameters (change from baseline in HAMD total scores and the proportion of responders-where response was defined as a $\geq$50% reduction from baseline in HAMD score or a HAMD score $\leq$8 at endpoint). However, trends in favour of paroxetine compared with placebo were seen across all the indices of depression (change from baseline in HAMD total [p=0.133], HAMD responders [p=0.112], CGI [p=0.094] and K-SADS [p=0.065] scores) and statistically significant differences from placebo were observed in the proportion of patients in remission (defined as a HAMD score of $\leq$8 at endpoint). In general, the response to imipramine was similar to that for placebo. The 6 month extension phase has now completed and is scheduled to report at the end of 1998.

Study 377 was a 12 week placebo-controlled study, conducted in 276 adolescents with major depression. There was a high placebo response rate in this study and no statistically or clinically significant differences from placebo were observed on either of the primary efficacy variables (proportion of patients achieving a $\geq$50% reduction from baseline in total MADRS scores and change from baseline in the K-SADS-L depressive subscale score). The only differences from placebo (secondary efficacy variables) were seen in a subgroup of patients who were $\geq$16 years of age.

Possible explanations for the high placebo response include;

Prepared by CMAt -Neurosciences

1) The large number of study visits
2) the duration of the assessments
3) The fact that concomitant psychotherapy was not excluded
4) Question marks about the adequacy of using currently available diagnostic criteria and rating scales in younger patients
5) Adolescents may be more susceptible to a placebo effect
6) Developmental issues. Children and adolescents may respond in a pharmacologically different manner due to quantitative and/or qualitative differences in neurotransmitter/receptor systems.

Conclusions from these studies:

- There were no differences in the safety profile of Seroxat/Paxil in adolescents when compared to that already established in the adult population

- The efficacy data from the above clinical trials are insufficiently robust to support a regulatory submission and label change for this patient population.

OTHER DATA:

Ongoing studies: SB France are conducting a locally funded double-blind, comparative study of Seroxat/Paxil with clomipramine in adolescents with major depression (Study 511). In addition, a study in adolescents with OCD (Study 453) is underway in the US. This study comprises a 16 week open label Seroxat/Paxil treatment phase, followed by double-blind, randomisation to paroxetine or placebo for a further 16 weeks of treatment. The regulatory acceptability of these 2 studies needs to be established.

Published data: A review of the literature shows that 2 studies assessing the use of paroxetine in the treatment of 34 adolescents and children with depression have been published (Rey-Sanchez and Gutierrez-Cesares, 1997; Findling et al; 1996).

The first study (Rey-Sanchez and Gutierrez-Cesares, 1997) was a retrospective survey of data from 25 adolescents (aged 13-17 years) treated with paroxetine. Patients were diagnosed according to ICD 10 criteria. In 13 of the patients unipolar major depression was not the primary diagnosis. 17 patients received paroxetine as a monotherapy, 8 also received concomitant psychotropic medications (n=7 benzodiazepines, n=1 haloperidol). Paroxetine was administered at doses of 10mg (14 patients) or 20mg/day (11 patients). No specific depression rating scales were used, response was based on clinical judgement. 76% patients

had a satisfactory response (11 complete remission, 8 improved with residual symptoms). A lack of satisfactory response in was observed in 6 (24%) patients. Eight patients reported side effects (somnolence or sleep disorders n=6, asthenia n=4, nausea n=3, tachycardia n=2, diarrhea n=2, headache n=2, orthostatic hypotension n=1, restlessness n=1). Two patients were withdrawn due to one due to anxiety, one due to hypotension and dizziness)

The second study (Findling et al; 1996) was conducted in 9 patients aged between 7-15 years (children and adolescents) meeting DSM IV criteria for a major depressive disorder. Symptomatology was assessed using HAM-D for subjects aged 13 to 15 years, and the childhood depression rating scale (CDRS) subjects aged 12 or younger. Paroxetine was initially given at a dose of 10mg/day. This was escalated to 20mg/day if the patient had not responded after 4 weeks of treatment. 8/9 patients responded to treatment with paroxetine. Three patients had complete remission, 5 patients had a >50% reduction in total CDRS score from baseline. CGI improved in all patients. One patient withdrew from the study at week 2 due to an adverse experience. This patient was found to have elevated serum paroxetine levels and was a poor 2D6 metaboliser. Assessment of pharmacokinetic parameters in this study showed that paroxetine had a similar half life to that reported in the adult population (15.7h [sd 9.0h] vs 24h, respectively).

COMPETITOR ACTIVITIES:

Lilly are believed to be in near to completing their phase III clinical trials in adolescent depression. One relatively large placebo-controlled 8 week study with an open 12 month follow-up period conducted in 96 patients (aged 8-18 years) has recently been published (Emslie et al; 1997 and 1998). These data show that 56% (27/48) patients on fluoxetine (20mg/day) compared with 33% (16/48) patients on placebo were rated as much or very much improved on the CGI at Week 6 (p=0.02. In the 12 month follow-up period, 85% (n=74) patients recovered from the depressive episode (47 on fluoxetine, 22 on placebo and 5 on other antidepressants or lithium). Twenty nine (39%) of the patients (36% of those who had recovered on fluoxetine [17/47] and 41% of those who had recovered on placebo [9/22] had a recurrence of depression during the 12 month follow-up (a higher recurrence rate than seen in adults). Other published data on fluoxetine are from small open studies or individual case reports (Colle et al; 1994).

Pfizer already have positive data (including PK data) and are licenced in the US for the treatment of adolescent OCD. In addition, Pfizer are also believed to be conducting clinical trials in adolescent depression. Available published data are

limited, derived from small open studies in adolescent depression (McConville et al; 1996; Tierney et al; 1995)

TARGET

To effectively manage the dissemination of these data in order to minimise any potential negative commercial impact.

PROPOSALS

- Based on the current data from Studies 377 and 329, and following consultation with SB country regulatory and marketing groups, no regulatory submissions will be made to obtain either efficacy or safety statements relating to adolescent depression at this time. However data (especially safety data) from these studies may be included in any future regulatory submissions, provided that we are able to go on and generate robust, approvable efficacy data. The rationale for not attempting to obtain a safety statement at this time is as follows;

  i) regulatory agencies would not approve a statement indicating that there are no safety issues in adolescents, as this could be seen as promoting off-label use

  ii) it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.

- Positive data from Study 329 will be published in abstract form at the ECNP (Paris, November 1998) and a full manuscript of the 329 data will be progressed.

- The regulatory acceptability of Studies 511 and 453 and any other data in this patient population will continue to be investigated.

Appendix 2

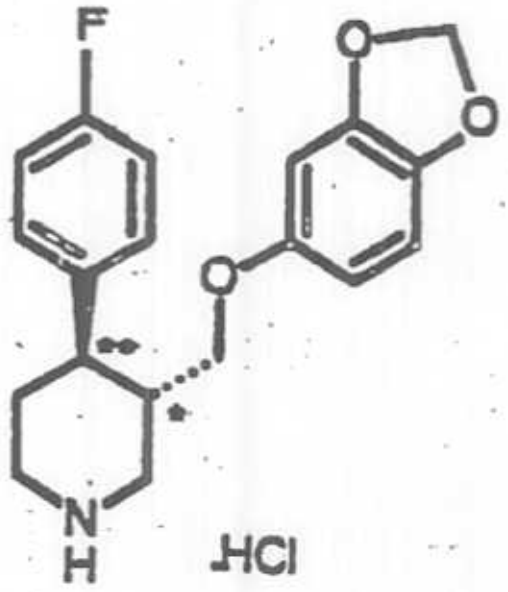
Appendix 3

REVIEW AND EVALUATION OF CLINICAL DATA

ORIGINAL NDA 20-031

PAROXETINE (AROPAX®)

SAFETY REVIEW



Reviewer: Martin Brecher M.D., D.M.Sc.

Sponsor: SmithKline Beecham Pharmaceuticals

Date: June 19, 1991

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bed. The frequency of pulmonary embolism in the medically ill population, the infrequency of embolism in the paroxetine population, the absence of other embolic events and the absence of other manifestations of coagulopathy render it difficult to attribute these 2 fatal pulmonary emboli to paroxetine.

Deaths-Suicide.
An additional 15 patients, all enrolled in European trials, (7 paroxetine, 1 imipramine, 1 fluvoxamine, 1 amitriptyline and 5 placebo) committed suicide. The method was provided in 10 of the cases, but none of the deaths was attributable to overdosage of paroxetine. The minimum lethal dose is therefore unknown. Two of the five placebo suicides occurred during run-in.

A 58 year old woman receiving paroxetine (Belgian open study 2206.005 patient Vol. 1.408 p.281) committed suicide by hanging in the fifth month of treatment. No further information is available.

A 42 year old woman (Study DFC124 patient Vol. 1.416 p. 217) on an unstated dose of paroxetine took a fatal overdose of doxepin.

A patient on placebo (Vol. 1.416, p.120) committed suicide.

A 50 year old man (Study MDUK13 patient Vol. 1.411 p. 290) on 30 mg/d paroxetine committed suicide by hanging on the 144th day of treatment. All adverse events had resolved by the time of the suicide.

An 18 year old woman (Study 29060 patient Vol. 1.414 p. 199) discontinued paroxetine on day 38 and committed suicide by overdosage on day 44. She received Valium from day 32. Details regarding the pills consumed were not provided.

A 56 year old woman (Study HP/82/47 patient Vol. 1.414 p. 344) on 30 mg paroxetine killed herself by drowning on day 47.

A 51 year old man (Protocol 058/022) on an unknown dose of paroxetine committed suicide in June 1990.

A 66 year old man (Study 29060 patient Vol. 1.415 p. 230) received clomipramine for 6 weeks before being switched to fluvoxamine. One month later he committed suicide by hanging.

A 36 year old man (Study HP/83/67 patient Vol. 1.415 p. 276) who improved on 150 mg/d amitriptyline committed suicide by undescribed means.

A 58 year old man (DFC124 patient Vol 1.416 p. 226) receiving imipramine killed himself with a firearm.

A 49 year old man (7119.009 Vol. 1.408 p.295) committed suicide during the placebo run-in phase.

A 43 year old man (Study DFC119 patient Vol. 1.416 p. 152) committed suicide during the placebo run-in of the study.

Patient (Annual report) received placebo and committed suicide by drowning.

An 80 year old man (Annual report, patient# on placebo committed suicide by hanging.

A 58 year old woman (Study 29060/083 patient Update Vol 24.3 p. 1) committed suicide by hanging on day 8 of paroxetine treatment.

Deaths-Other Causes

A 55 year old woman (patient Vol. 1.408, p. 287) being treated with paroxetine was murdered.

Suicide Attempts

59 additional patients attempted suicide. 14 of these patients were enrolled in U.S. trials; the remainder were enrolled in Europe. The 14 U.S. patients included 12 on paroxetine, 1 on imipramine and 1 on placebo. The 45 foreign suicide attempts included 30 paroxetine patients, 13 patients who received an active control and 2 placebo patients. The largest overdose of paroxetine was 850 mg. This patient was admitted to the hospital in a semi-obtunded state and thereafter showed steady improvement. The next largest overdose was 420 mg which resulted in admission to the hospital with symptoms of mydriasis, dry mouth and sinus tachycardia. The patient was discharged the following day. Another patient took a 360-400 mg overdose of paroxetine. This patient was obtunded when admitted to the Emergency Room, but was alert 7 hours later.

42 of the 59 suicide attempts (71.8%) were made by patients on paroxetine who comprised 63.5% of the patients in the Phase II-III trials. However the paroxetine patients were exposed and observed for longer durations rendering the distribution of suicide attempts unremarkable.

Overview of Suicidality

Given current concern that a small proportion of depressed patients may develop unprecedented, obsessive and severe suicidal ideation on serotonin reuptake inhibitors we asked the sponsor to analyze the data base for emerging suicidality. The sponsor submitted an analysis of the NDA data base of 4,668 patients of whom 2963 received paroxetine, 1151 received an active control and 554 received placebo. Suicidality was counted as an adverse event if the following adverse events were noted in the clinical record: suicidal ideation, suicide risk, ideas of suicide, suicidal thoughts, suicidal tendency, parasuicidal tendency, felt suicidal, became suicidal, suicidal feelings and suicidal threats. Table 13 lists the results for the three treatment groups.

TABLE 13
Suicidality in Paroxetine Clinical Trials

	Paroxetine N=2963 1008 P.E.Y.*	Placebo N=554 72 P.E.Y.	Active Control N=1151 218 P.E.Y.
Completed Suicides			
No. (%)	5 (0.17)	2 (0.36)	3 (0.26)
No./P.E.Y.	0.005	0.028	0.014
Attempted Suicides			
No. (%)	40 (1.3)	6 (1.1)	12 (1.0)
No./(P.E.Y.)	0.040	0.083	0.055
Suicidality Reported as an Adverse Event			
No. (%)	13 (0.4)	2 (0.4)	5 (0.4)
No./P.E.Y.	0.013	0.028	0.023

* P.E.Y. stands for Patient Exposure Years

The values for paroxetine did not exceed those of the other two groups for any of the 6 measures.

The sponsor also estimated the frequency of emergent suicidal ideation by counting the number of patients with a baseline score of 0 or 1 on the Hamilton Depression Scale suicide item (item #3) who developed significant suicidal ideation at any point during a six week trial as measured by a score of 3 or 4 on the suicide item. The results of this analysis were:

Paroxetine N=1659 N (%)	Placebo N=331 N (%)	Active Control N=683 N (%)
29 (1.7)	5 (1.5)	9 (1.3)

Parox. vs. Placebo p >0.9; Parox. vs. Active p =0.59; Active vs. Placebo p =0.78

Although the instruments available may not be ideal to capture the elusive clinical events reported by Teicher in 6 patients, there is no signal in this large data base that paroxetine exposes a subset of depressed patients to additional risk for suicide, suicide attempts or suicidal ideation.

Myocardial Ischemia and Congestive Failure

Patient (Vol. 1.410 p. 56), a 47 year old man, was discontinued from 50mg/d on the 103rd day of treatment after an ECG revealed T wave changes (isoelectric T-wave in leads V4-6) compatible with myocardial ischemia. The patient did not have cardiac symptoms and lab values and a chest X-ray remained normal. No ischemic changes were noted on stress testing two weeks after discontinuation. The consulting cardiologist considered the patient's abnormal repolarization to be a normal variant.

Patient who received 40 mg/d paroxetine for 39 months had an angiographically confirmed anterior wall myocardial infarction. He had a history of smoking and hypercholesterolemia. This case was not reported in the list of dropouts and was discovered in the sponsor's correspondence file (Vol. 12 of 14, p. 3003).

The sponsor's proposed listing of other events, particularly for the nervous and gastrointestinal systems which are the major loci of paroxetine's adverse events, contain numerous other errors of commission and omission. These lists contain items which have already been listed in the previous table and omit other adverse events which should be listed. The sponsor will need to revise these lists.

SUMMARY

Review of the well organized safety database did not reveal any serious toxicity attributable to paroxetine. The side effect profile of paroxetine is similar to that of selective serotonin reuptake inhibitors and different from that of the tricyclic antidepressants. The accompanying efficacy review found paroxetine to be an effective antidepressant. Together the safety and efficacy data allow the conclusion that paroxetine is safe and efficacious and approvable for marketing.

Martin Brecher

Martin Brecher, M.D., D.M.Sc.
June 19, 1991

cc: Original NDA, 20-031
HFD-120
HFD-120/P Leber
/T Laughren
/M Brecher
/P David

10-5-92

I have reviewed Dr. Brecher's findings and, in addition, I have reviewed the 2-13-92 safety update that increased the population of paroxetine exposures in premarketing studies to approximately 5100 patients. The safety and efficacy findings for paroxetine were presented to the PDAC on this date (10-5-92), and they unanimously agreed that paroxetine has been demonstrated to be safe and effective. I agree that these data do not reveal any safety findings that would preclude the approvability of paroxetine for use in depression. My written review of the safety update, will follow shortly, and I will provide more detailed comments on safety issues in my supervisory memo, also to follow. I have prepared the clinical sections of the draft SBA and the draft labeling that will accompany the approvable package.

Thomas P. Laughren, MD
Group Leader, PDP

Appendix 4

AUG 16 1990

Statistical Review and Evaluation
(Addendum)

NDA #: 19-839/Drug Class 1C AUG 14 1990

Applicant: Pfizer Central Research

Name of Drug: Sertraline HCl

Indication: Depression

Clinical Reviewer: Hillary Lee, Ph.D. (HFD-120)

According to the clinical reviewer, there are reasons to look at the results of Study 104 excluding Center 13 (Investigator Cohn). Accordingly, analyses were done excluding Center 013 to the "All Patients" data set supplied by the sponsor on the computer. The following p-values were obtained by applying SAS "PROC TTEST" (Tukey's T-test was not applied since we are looking into only the sertraline vs placebo comparison), and there seems to be no reason to change our original conclusions.

Change From Baseline in HAMD Total (Excluding Center 013)

Week		Placebo		Sertraline		
		Mean	N	Mean	N	P-Value
3	OC	-7.31	95	-9.15	92	.051
	LOCF	-6.49	113	-8.02	113	.080
5	OC	-9.36	85	-12.38	78	.010
	LOCF	-7.75	113	-10.41	113	.010
6	OC	-9.58	76	-12.58	76	.011
	LOCF	-7.79	113	-10.69	113	.006
7	OC	-9.32	76	-14.01	69	.0001
	LOCF	-7.56	113	-11.20	113	.0005
8	OC	-10.09	69	-14.54	70	.0003
	LOCF	-7.84	113	-11.53	113	.0005

Change From Baseline in HAMD Dep. Item 1 (Excluding Center 013)

Week		Placebo		Sertraline		
		Mean	N	Mean	N	P-Value
3	OC	-.89	95	-1.24	92	.029
	LOCF	-.79	113	-1.09	113	.042
5	OC	-1.26	95	-1.62	78	.059
	LOCF	-.98	113	-1.35	113	.021
6	OC	-1.18	76	-1.63	76	.015
	LOCF	-.97	113	-1.38	113	.010
7	OC	-1.07	76	-1.90	69	.0001
	LOCF	-.86	113	-1.48	113	.0002
8	OC	-1.23	69	-1.94	70	.0002
	LOCF	-.96	113	-1.53	113	.0006

Change From Baseline in CGI Severity (Excluding Center 013)

Week		Placebo		Sertraline		
		Mean	N	Mean	N	P-Value
3	OC	-.75	95	-1.14	92	.010
	LOCF	-.65	113	-.96	113	.023
5	OC	-1.16	85	-1.67	76	.016
	LOCF	-.87	113	-1.37	113	.006
6	OC	-1.28	76	-1.84	77	.005
	LOCF	-.97	113	-1.47	113	.005
7	OC	-1.18	76	-2.10	68	.0001
	LOCF	-.90	113	-1.57	113	.0002
8	OC	-1.32	69	-2.21	70	.0001
	LOCF	-.98	113	-1.65	113	.0005

Japo Choudhury 8-14

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius 8-14-90

Dr. Dubey 8-14-90

cc:
Orig. NDA 19-839
HFD-120
HFD-120/CSO
HFD-120/Dr. Leber
HFD-120/Dr. Laughren
HFD-120/Dr. Lee
HFD-713/Dr. Choudhury
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Group 2 File
HFD-344/Dr. Lisook
Chron/

ajd/SERB/writenow/NDA19-839/8-13-90

This addendum consists of 5 pages.

JAN 31 1991

Statistical Review and Evaluation
(Addendum 2)

NDA #: 19-839/Drug Class 1C

Applicant: Pfizer Central Research

Name of Drug: Sertraline HCl

Indication: Depression

Documents Reviewed: Amendment of 9-14-90, Enclosures #3 and #4

Clinical Reviewer: Hillary Lee, Ph.D. (HFD-120)

A. Enclosure #4 (HAMD Subscale Analysis)

Some of the items included in the HAMD Total may be confounded with adverse effects rather than being one hundred percent representative of efficacy. Because of this confounding, the clinical reviewer, the group leader (clinical) and I requested of the sponsor analyses excluding items 4 (early insomnia), 5 (middle insomnia), 6 (late insomnia), 9 (agitation), 10 (psychic anxiety), 11 (somatic anxiety), 12 (somatic symptoms - GI) and 13 (somatic symptoms-general). The total of the reduced set of items has been referred to as Subscale 5 in the sponsor's amendment. The sponsor's analyses are presented in Appendix A of this report, as are the original results for comparison.

Reviewer's Comments

The 100mg group is seen to show the most consistent evidence of efficacy, with both OC and LOCF analyses at least marginally significant (two-sided P<.10) for all analyses done at Week 3 or later. These analyses at weeks 4, 5, 6, as well as "last visit" were statistically significant by both OC and LOCF analyses (two-sided P<.05).

Conclusion

Results for the 100mg group are highly significant for all weekly analyses after Week 3 (p<.016) and at least marginally significant at Week 3. These results are more persuasive than the original analyses of the entire HAMD-scale (see Appendix A).

B. Enclosure #3 (Analysis of Suicide Attempts Data)

The overall incidence rates of suicide attempts in sertraline therapeutic depression studies, as provided originally by the sponsor, are presented in Appendix B. The incidence rate (per patient-year) of suicide attempts for sertraline is .0177 compared

to .0239 for placebo according to this original analysis. Two of the sertraline attempts resulted in completed suicide; apparently none of the placebo attempts resulted in completed suicide.

It was seen from the case report forms that 3 out of the 5 suicide attempts shown under placebo occurred before the comparative double-blind phase of the studies started. Excluding those 3 suicide attempts (and hence also the washout exposure time), the new incidence rate (per patient-year) of suicide attempts for placebo is .0137 (sertraline rate remains .0177, the same as before). The sponsor utilized the number of suicide attempts per person-year of exposure in its analysis. In response to our request for a life table analysis the sponsor stated that sufficient data were not available (some studies are overseas) for the entire data base to permit such an analysis and, in addition, provided details of the statistical method followed in the original statistical analysis. In the absence of the complete information needed for a life-table analysis, this methodology seems reasonable.

The sponsor also provided (at our request) an analysis comparing suicide attempt rates for the comparative double-blind phase only (omitting the wash-out period data). The analysis supplied by the sponsor (Fax Transmittal on Nov. 7, 1990) contained an error in calculation of the appropriate p-values. The correct p-values are .54 for the new data set (omitting the wash-out period) and .80 for the original data set. (Dr. David Salsburg of Pfizer confirmed that the sponsor's calculations were incorrect due to the use of the wrong tail of the distribution.)

The sponsor also analyzed shifts to greater suicide tendency among patients with none at baseline by comparing the proportions of patients in the sertraline and placebo groups having a HAMD Item 3 score of 0 or 1 at baseline who shifted to a score of 3 or 4, where 0=absent, 1=feels life is not worth living, 2=wishes he were dead or any thoughts of possible death to self, 3=suicide ideas or gestures, 4=attempts at suicide. From Table 3 of Enclosure #3, these numbers (%) are 3/136 (2.2%) for sertraline and 1/51 (2.0%) for placebo. This analysis clearly does not suggest a concern.

<u>Conclusion</u>

Based on the examination of rates of clinical suicide attempts, rates of events defined by baseline to endpoint shifts in HAMD Item 3 (suicide) scores, and mean baseline to endpoint changes in HAMD Item 3 scores presented in Enclosure #3, this reviewer does not see any statistical evidence to indicate a concern for sertraline with respect to suicidal tendencies in the therapeutic depression trials.

REFERENCES: Barlow, R.E., Bartholomew, D.J., Bremner, J.M., and Brunk, H.D. (1972)
Statistical Inference Under Order Restrictions, John Wiley & Sons, New York, Chapter 6, Isotonic Tests for Goodness of Fit.

Lehmann, E. L. (1959) Testing Statistical Hypotheses, John Wiley & Sons, New York, Section 4.5, Comparing Two Poison or Binomial Populations.

Japo Choudhury 1-28-91
Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius BEN 1-29-91

Dr. Dubey 1-30-91

cc:
Orig. NDA 19-839
HFD-120
HFD-120/CSO
HFD-120/Dr. Leber
HFD-120/Dr. Laughren
HFD-120/Dr. Lee
HFD-713/Dr. Choudhury
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Group 2 File
HFD-344/Dr. Lisook
Chron.

meg/SERB/wp/NDA-19-839/1-7-91

This addendum consists of 3 pages of text and 2 appendices.

HAMD SUBSCALE ANALYSES - SERTRALINE PROTOCOL 103
****** OC ******

TREATMENT COMPARISON RESULTS FOR CHANGE FROM BASELINE IN HAMD SUBSCALE 6 BY VISIT - OC

VISIT	TREATMENT COMPARISON	TRT EFFECT#	95% C. I.	1-SIDED P-VALUE	SIG
WEEK 1	SER VS PBO	-0.03	(-0.84, 0.78)	0.469	
	50 VS PBO	0.60	(-0.48, 1.48)	0.157	
	100 VS PBO	-0.67	(-1.68, 0.32)	0.091	.
	200 VS PBO	0.07	(-0.96, 1.09)	0.446	
WEEK 2	SER VS PBO	-0.59	(-1.65, 0.47)	0.138	
	50 VS PBO	-0.17	(-1.43, 1.10)	0.398	
	100 VS PBO	-0.74	(-2.03, 0.64)	0.128	
	200 VS PBO	-0.86	(-2.28, 0.63)	0.112	
WEEK 3	SER VS PBO	-1.65	(-2.76, -0.35)	0.006	..
	50 VS PBO	-0.86	(-2.28, 0.58)	0.121	
	100 VS PBO	-1.88	(-3.35, -0.40)	0.006	..
	200 VS PBO	-1.92	(-3.50, -0.34)	0.009	..
WEEK 4	SER VS PBO	-1.74	(-3.02, -0.46)	0.004	..
	50 VS PBO	-1.11	(-2.61, 0.38)	0.072	.
	100 VS PBO	-1.96	(-3.50, -0.40)	0.007	..
	200 VS PBO	-2.10	(-3.82, -0.50)	0.006	..
WEEK 5	SER VS PBO	-1.99	(-3.12, -0.85)	0.000	...
	50 VS PBO	-1.38	(-2.71, -0.05)	0.021	.
	100 VS PBO	-2.30	(-3.69, -0.91)	0.000	...
	200 VS PBO	-2.27	(-3.72, -0.82)	0.001	..
WEEK 6	SER VS PBO	-1.76	(-2.99, -0.51)	0.003	..
	50 VS PBO	-0.76	(-2.20, 0.68)	0.150	
	100 VS PBO	-2.43	(-3.90, -0.90)	0.001	..
	200 VS PBO	-2.06	(-3.66, -0.44)	0.006	..
LAST VISIT	SER VS PBO	-1.66	(-2.81, -0.49)	0.003	..
	50 VS PBO	-1.03	(-2.23, -0.42)	0.006	..
	100 VS PBO	-1.76	(-3.16, -0.34)	0.008	..
	200 VS PBO	-1.38	(-2.81, 0.06)	0.030	.
70 % RULE	SER VS PBO	-1.48	(-2.69, -0.27)	0.008	..
	50 VS PBO	-0.83	(-2.27, 0.60)	0.127	
	100 VS PBO	-1.78	(-3.24, -0.28)	0.010	.
	200 VS PBO	-1.86	(-3.46, -0.26)	0.011	.

based on least squares means (LSMEANS)

LEGEND OF SIGNIFICANCE:

BLANK		p) 0.10
.	0.05	< p < 0.10
*	0.01	< p < 0.05
**	0.001	< p < 0.01
***		p < 0.001

SUBSCALE 6 = HAMD TOTAL - ITEM 4 (INSOMNIA - EARLY)
6 (INSOMNIA - MIDDLE)
8 (INSOMNIA - LATE)
9 (AGITATION)
10 (ANXIETY - PSYCHIC)
11 (ANXIETY - SOMATIC)
12 (SOMATIC SYMPTOMS - GI)
13 (SOMATIC SYMPTOMS - GENERAL)

HAMD SUBSCALE ANAL
***

TREATMENT C
IN HAMD SUBSC

VISIT	TREATMENT COMPARISON	EFF
WEEK 1	SER VS PBO	
	50 VS PBO	
	100 VS PBO	
	200 VS PBO	
WEEK 2	SER VS PBO	
	50 VS PBO	
	100 VS PBO	
	200 VS PBO	
WEEK 3	SER VS PBO	
	50 VS PBO	
	100 VS PBO	
	200 VS PBO	
WEEK 4	SER VS PBO	
	50 VS PBO	
	100 VS PBO	
	200 VS PBO	
WEEK 5	SER VS PBO	
	50 VS PBO	
	100 VS PBO	
	200 VS PBO	
WEEK 6	SER VS PBO	
	50 VS PBO	
	100 VS PBO	
	200 VS PBO	
LAST VISIT	SER VS PBO	
	50 VS PBO	
	100 VS PBO	
	200 VS PBO	
70 % RULE	SER VS PBO	
	50 VS PBO	
	100 VS PBO	
	200 VS PBO	

based on least squares

LEGEND OF SIGNIFICANCE:

SUBSCALE 6 = HAMD TOTAL -

Appendix A

ANALYSIS OF TREATMENT EFFECTS BY WEEK FOR CHANGE IN HAMD TOTAL SCORE - OBSERVED CASES

VISIT	TREATMENT COMPARISON	TRT EFFECT#	95% C. I.	P-VALUE	SIG
WEEK 1	SER VS P	0.36	(-0.95, 1.67)	0.293	
	50 VS P	0.77	(-0.81, 2.35)	0.170	
	100 VS P	-0.40	(-1.99, 1.19)	0.311	
	200 VS P	0.72	(-0.93, 2.36)	0.196	
WEEK 2	SER VS P	-1.00	(-2.88, 0.71)	0.117	
	50 VS P	-1.08	(-3.20, 1.07)	0.164	
	100 VS P	-1.11	(-3.20, 1.00)	0.150	
	200 VS P	-1.00	(-3.44, 1.20)	0.186	
WEEK 3	SER VS P	-2.38	(-4.29, -0.81)	0.012	*
	50 VS P	-2.14	(-4.51, 0.22)	0.038	*
	100 VS P	-2.43	(-4.87, 0.01)	0.026	*
	200 VS P	-2.32	(-4.94, 0.31)	0.042	*
WEEK 4	SER VS P	-2.02	(-4.00, -0.35)	0.012	*
	50 VS P	-1.94	(-4.60, 0.72)	0.076	*
	100 VS P	-2.57	(-5.33, 0.19)	0.034	*
	200 VS P	-3.36	(-6.31, -0.41)	0.018	*
WEEK 5	SER VS P	-2.31	(-4.30, -0.32)	0.012	*
	50 VS P	-1.62	(-3.96, 0.70)	0.086	*
	100 VS P	-2.78	(-5.22, -0.35)	0.013	*
	200 VS P	-2.62	(-5.06, 0.02)	0.026	*
WEEK 6	SER VS P	-2.88	(-4.85, -0.74)	0.004	**
	50 VS P	-1.82	(-3.78, 1.07)	0.138	
	100 VS P	-3.64	(-6.37, -1.31)	0.002	**
	200 VS P	-3.28	(-5.98, -0.57)	0.009	**
LAST VISIT	SER VS P	-2.27	(-4.31, -0.23)	0.015	*
	50 VS P	-3.01	(-5.48, -0.54)	0.009	**
	100 VS P	-2.18	(-4.66, 0.30)	0.042	*
	200 VS P	-1.81	(-4.14, 0.91)	0.106	

legend of significance: blank 0.10 < p
* 0.05 < p < 0.10
** 0.01 < p < 0.05
*** p < 0.001

based on lsmeans

ANALYSIS OF TREATMENT EFFECTS BY WEEK FOR CHANGE IN HAMD TOTAL SCORE - LOCF

VISIT	TREATMENT COMPARISON	TRT EFFECT#	95% C. I.	P-VALUE	SIG
WEEK 1	SER VS P	0.46	(-0.83, 1.76)	0.241	
	50 VS P	0.83	(-0.73, 2.40)	0.148	
	100 VS P	-0.33	(-1.91, 1.26)	0.342	
	200 VS P	0.88	(-0.78, 2.50)	0.141	
WEEK 2	SER VS P	-0.59	(-2.24, 1.06)	0.241	
	50 VS P	-1.19	(-3.19, 0.80)	0.120	
	100 VS P	-0.88	(-2.88, 1.13)	0.195	
	200 VS P	0.30	(-1.76, 2.36)	0.387	
WEEK 3	SER VS P	-1.14	(-2.93, 0.66)	0.107	
	50 VS P	-2.14	(-4.32, 0.03)	0.026	*
	100 VS P	-1.22	(-3.48, 0.96)	0.136	
	200 VS P	-0.84	(-2.27, 2.19)	0.487	
WEEK 4	SER VS P	-1.07	(-3.02, 0.28)	0.046	*
	50 VS P	-2.26	(-4.62, 0.10)	0.030	*
	100 VS P	-1.92	(-4.29, 0.44)	0.055	*
	200 VS P	-0.83	(-3.24, 1.59)	0.250	
WEEK 5	SER VS P	-1.83	(-3.80, 0.14)	0.034	*
	50 VS P	-2.56	(-4.94, -0.17)	0.018	*
	100 VS P	-1.88	(-4.22, 0.57)	0.067	*
	200 VS P	-1.11	(-3.56, 1.34)	0.186	
WEEK 6	SER VS P	-2.00	(-4.12, -0.03)	0.023	*
	50 VS P	-2.87	(-5.16, -0.19)	0.017	*
	100 VS P	-2.87	(-4.66, 0.42)	0.061	*
	200 VS P	-1.48	(-4.02, 1.06)	0.126	
LAST VISIT	SER VS P	-2.27	(-4.31, -0.23)	0.015	*
	50 VS P	-3.01	(-5.48, -0.54)	0.009	**
	100 VS P	-2.18	(-4.66, 0.30)	0.042	*
	200 VS P	-1.81	(-4.14, 0.91)	0.106	

legend of significance: blank 0.10 < p
* 0.05 < p < 0.10
** 0.01 < p < 0.05
*** p < 0.001

based on lsmeans

Appendix B

Comparative Incidence Rates of Suicide Attempts in Sertraline Therapeutic Depression Studies

	Sertraline	Placebo	Active Control
Number of patients	2053	786	595
Number of patients - years exposure	507.9	209.0[1]	90.8
Number of suicide attempts	9	5	1
Incidence rates (per pt-yr) of suicide attempts	0.0177	0.0239	0.0110
Incidence rates (per 100 pt-yr) of suicide attempts	1.77	2.39	1.10
95% confidence limits[2] on incidence rates per 100 pt-yr	0.8-3.4	0.7-5.5	0.0-6.2

1 This figure includes 145.8 patient-years of double-blind placebo and 63.2 patient-years of single-blind placebo exposure.

2 The confidence limits per pt-yr were computed on the original proportions (e.g. 9/508) using the exact binomial distribution. The incidence rates and corresponding confidence limits were then each multiplied by 100 to give incidence rates and confidence intervals per 100 pt-yr.

Statistical Review and Evaluation
(Addendum 3)

MAR 2 9 1991

NDA #: 19-839/Drug Class 1C

Applicant: Pfizer Central Research

Name of Drug: Sertraline HCl

Indication: Depression

Clinical Reviewer: Hillary Lee, Ph.D. (HFD-120)

The test for dose response in Study 103 was done including the placebo group also. The primary purpose was to examine the efficacy of the test drug in an alternative way. To claim a dose-response, it may be argued that the placebo group should not be included in the test. The results (parallel to those given on page 9 of the original statistical review) excluding the placebo group are given below for HAMD Item 1, the variable which provided the strongest evidence for the efficacy of the test drug.

Change from Baseline in HAMD Item 1

	J^*	Prob. - Value
Week 3 LOCF	neg. value[b] (neg. value)[a]	> .5 (> .5)
OC	.702 (.541)[a]	.2414 (.2939)
Week 6 LOCF	-neg. value (.157)	> .5 (.4455)
OC	1.731 (1.779)	.0417 (.0375)

[a] - values given within parentheses are for the test excluding 200 mg dose group

[b] - a negative J^* is against the ordered alternative

Conclusion

Significant (<.05) p-values were obtained only for the observed cases analysis at Week 6 whether the 200 mg dose group is excluded or included. Therefore, there is not conclusive statistical evidence that a dose-response was observed.

Japo Choudhury 3-29-91

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius 3-29-91

Dr. Dubey 3-29-91

cc:
Orig. NDA 19-839
HFD-120
HFD-120/CSO
HFD-120/Dr. Leber
HFD-120/Dr. Laughren
HFD-120/Dr. Lee
HFD-713/Dr. Choudhury
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Group 2 File
HFD-344/Dr. Lisook
Chron
JChoudhury/jt/3-27-91/NDA 19-839/WP51 SRESER

This addendum consists of 2 pages.

Appendix 5

The IMR Patient Flow Model.

Principles of Drug Safety Regulation
All drug safety control systems must include these fundamental attributes:-

1) An effective feedback reporting system for suspected adverse drug reactions (ADRs) from actual use by a large majority of patients, to be received and continually assessed with bias to patient safety, by the Drug Safety Regulator.
2) An independent prediction of the number of patients using the drug and the range of harm to be expected in this population of patients.

Prediction is necessary because ADR feedback reporting is not mandatory. Tragically it is voluntary and therefore inadequate because medical professionals choose not to report ADRs for a variety of reasons. Consequently those agencies responsible for drug safety must continually review their confidence in the ADR feedback system itself with reference to the Prediction or forecast of patient numbers and harm.

Those who use lifts or elevators do appreciate that the feedback reports from the descent speed sensors to the brake control regulator are both mandatory and continuous throughout the descent. By comparison drug safety regulation is dysfunctional. The limited feedback to the regulator for several millions of patients in descent on SSRIs has only ever been voluntary, intermittent and generally dismissed by the Regulator, with catastrophic results.

Prediction measures are fundamental to all control systems that rely on voluntary/incomplete feedback and are widely used in other professions. In the regulating process, the agency must compare the prediction with the actual feedback however inadequate, and if these differ considerably, rigorous investigation is demanded until the reasons for the differences are understood. If the prediction cannot be faulted then an immediate regulatory action is required to secure public safety.

Personal research into the failure of drug safety control for SSRIs in the UK in the last 12 years soon exposed these fundamental flaws: - virtually no feedback of ADRs and the total absence of a prediction strategy for numbers of patients, drug dependants and drug induced suicides. The UK Medical Regulator has no idea how many patients are on drug, how many are at risk and what those risks are.

This requirement for a prediction model of patient flow and harm for SSRIs resulted in the design and development of the IMR Model System.

Principle of the IMR Model System.

The study of SSRIs indicates characteristic patterns of usage or tolerance, from the early weeks through to several years. The total quantity of medication that has been issued from the pharmacies is known in annual or quarterly increments. A very accurate method has been devised for converting consumption of medication, moderated by characteristic patient usage, into actual numbers of patients.

The phasing of patients in starting or leaving the drug in the short term or finding themselves dependant for many years, is handled with flexibility and without artificial constraint in the model. The model starts running from the year of introduction of the drug. It generates an image of the patient flow that is progressively updated, giving all the accumulating totals of those joining or leaving the drug as the years go by for the entire and growing national cohort.

Annual cohorts may be characterised individually, with a different usage profile, drop out rate and suicide rate, (e.g. patients in 1994 may differ from those 2001). The IMR model will also calculate the number of long term patients (LTP) dependant at any time and will give breakdowns of how many patients have been on drug for a given number of years.

There is considerable evidence that the danger of induced suicide or suicidal acts occurs in any dose transition with SSRIs, particularly in the first weeks of starting the drug, or when trying to stop after long use. The IMR model uses a range of suicide rates to calculate the total suicides induced in various combinations of depressed and anxious patients both when they start the drug and when they attempt to withdraw.

In summary, IMR will calculate any subtotals for any year and for the whole term: new patients, total patients treated, long term patients, drop outs (both short and long term), new long term patients, start drug suicides, withdrawal suicides.

The model logic, arithmetic, assumptions and implementation have been challenged in a series of extensive stress and sensitivity tests, designed to expose errors, adverse assumptions and to measure model response to variation of all input parameters. Independent assessments have been made at Universities and by the UK MHRA. No flaws in the logic and methodology of the IMR patient flow model system have been found.

IMR has been used to model the patient flow resulting from the use of paroxetine, fluoxetine and sertraline since introduction in several countries including the US.

Graham Aldred Pub IMR 5 February 14 2004