

Study 329

David Healy

Data Access, Data Access, Data Access

On all sides, in periodicals, academic journals, Op-Eds and on the web, there are demands from critics of the pharmaceutical industry for access to the data from clinical trials competing with good news stories from pharmaceutical companies about how they are working hard to go beyond the wildest data access dreams of researchers.

The struggle often comes wrapped in a story - the story of Tamiflu – how starting in 2009 Tom Jefferson and Peter Doshi and Cochrane Collaboration researchers stumbled on the fact that Roche, the makers of a supposedly anti-influenza medication, Tamiflu, had published misleading articles on its benefits leading governments worldwide to stockpile billions of dollars of a close to worthless and perhaps even dangerous drug.

Jefferson and Doshi's push for access to the data developed into a campaign that mobilized the British Medical Journal, JAMA and governments to call for access and ultimately seemingly led GlaxoSmithKline, GSK, to break ranks with other pharmaceutical companies and set up a portal through which they promised to give researchers what they wanted. Other companies the story goes have scrambled to follow suit.

But the Tamiflu story only starts to take shape 5 years after GSK were forced by a New York court as part of the resolution of a fraud case centering on Study 329, a clinical trial of Paxil undertaken in children, to post the "data" from a series of their trials on a company website. That posting contributed to another disaster for GSK - the discovery that its anti-diabetes drugs Avandia was killing people. Paxil and Avandia combined to land GSK with a \$3 Billion fine - the largest in US corporate history.

So why would GSK lead the bandwagon for more access to trial data? The real story of what happened contains clues but remains untold.

Study 329 began in 1994. Before plunging in, two pieces of information are critical. First, had the data from the trials of the SSRI antidepressants – Prozac, Paxil and Zoloft - been available from the get-go, these data would have demonstrated as of 1988 and for every succeeding year the use of these antidepressants led a doubling of suicidal acts compared to placebo in all age groups.

Second, in 1990 Martin Teicher and colleagues in Boston reported a compelling set of challenge-dechallenge descriptions of suicidality triggered by Prozac in adults and later that year the same authors reported a completed suicide in a 14 year old boy being treated with Prozac for obsessive-compulsive disorder (OCD).

Phase 1: 1994-2004

Study 329

Paroxetine was approved for marketing in the United States in 1992. It was standard at the time for an FDA approval to recommend that trials also be undertaken in children to test for safety.

The first protocol for Study 329 was drawn up in 1992. This trial was to be undertaken in adolescents and was designed to compare paroxetine (Paxil - called Seroxat in the UK) with imipramine, the very first antidepressant, and placebo. The study commenced in 1994, with the last patient recruited in 1997 and the last patient finishing the continuation phase in 1998.

Study 329 was published in July 2001 in the journal with the highest impact factor in child psychiatry – the Journal of the American Association of Child and Adolescent Psychiatrists. It had a distinguished authorship line, with 22 authors. The names of Martin Keller, Neil Ryan, Rachel Klein, Stan Kutcher, Boris Birmaher, Harold Koplewicz, Gabrielle Carlson, Graham Emslie, Barbara Geller and Karen Wagner were then among the most distinguished names in US psychiatry.

Keller's article reported that paroxetine was safe and effective in adolescents and children.

At most major psychiatric meetings in 2002, GlaxoSmithKline had a considerable presence with sponsored symposia featuring the role of paroxetine in the treatment of adolescent and adult depression and anxiety.

In 2002, Prozac had just gone off patent and Paxil was competing with Zoloft to be the best-selling antidepressant in the world. GSK had their sights on \$2 billion a year.

On October 7th 2002, three days before World Mental Health Day, the front cover of Newsweek featured an unhappy teenage girl and a strapline – “3 million kids suffer from it. What can you do. Teen depression.”

The message was that depression would cost children their careers, their relationships, their lives and if not treated it would lead to drug abuse and other problems. But fortunately Prozac had just been approved for the treatment of children and Paxil and Zoloft were about to be approved for teenage depression.

On October 10th 2002, World Mental Health Day and the fortieth anniversary of the signing of the 1962 amendments to the FDA Act, the US Food and Drug Administration (FDA) sent a letter to GlaxoSmithKline which stated:

“we have completed the review of this application [GlaxoSmithKline's application to have Paroxetine approved for paediatric use] and it is approvable”.

Secrets of Seroxat – Perils of Paxil

In June of 2001, a month before the publication of Study 329, a jury in Cheyenne Wyoming found GSK liable for the death of Donald Schell and his family because of the effects of Paxil. In August 2001 a Paxil withdrawal class action was filed in California.

Alerted by these developments, in September 2001 Shelley Jofre of BBC's Panorama team began exploring the possibility of a program dealing with the SSRI group of drugs. In early 2002, Panorama committed to a program that would focus on the biggest drug company in the world, then based in the United Kingdom – GlaxoSmithKline – and their best-selling drug – Seroxat (Paxil).

Some of the initial ideas for the program failed to materialise. Jofre had been reading Study 329 and was struck by the number of children in the study reported as having become emotionally labile on Paxil.

She attended the American Psychiatric Association (APA) meeting in Philadelphia in May 2002 where she met with Neil Ryan, one of the authors of Study 329. There she questioned him specifically about emotional lability.

Ryan contacted GSK immediately after the meeting to let them know that there was a reporter asking questions. He gave an evasive answer on camera to Jofre. She followed up with an email. He answered but did not clarify what was meant by emotional lability.

The first Panorama program The Secrets of Seroxat aired on October 13th 2002 – three days after World Mental Health Day (transcript available from author). The program covered suicidality on and dependence and addiction to Paxil and the testing of the drug in children.

Among the highlights was a set-piece between Jofre and Alastair Benlow, the head of European clinical psychiatry for GSK. Jofre put it to him that Paxil was making children suicidal who in response stated:

“There are a number of allegations that you made there, none of which are correct.

In terms of whether we think Seroxat should be made available to children? Absolutely. 2% of children, 4% of adolescents would develop depression. The adolescents are at particular risk of suicide. Suicide in adolescents is the third leading cause of death.

The vast majority of these patients did not have side effects significant enough to withdraw from treatment. The reality is that in this population depression is an extremely serious condition and in many cases leads to suicide”.

It is possible to level criticisms at the program. Were the lighting and camera angles more sympathetic to one side of the argument than the other? Did the editing create apparent shiftiness in decent people with no case? But it is difficult to deny that the questions Jofre asked needed to be asked, and somewhat disturbing that it was someone with no background in the issues who ended up asking them.

Emotional Lability

On August 28th 2002, six weeks before World Mental Health Day, two US plaintiff lawyers, Don Farber and Skip Murgatroyd, then prosecuting Paxil civil cases, had a meeting with the FDA's Steve Galson, deputy director of drug evaluation and research. Farber had initiated the FDA meeting, claiming plaintiffs' were in possession of Paxil data showing the drug's suicidal adverse events were more frequent and serious than GSK had acknowledged. Galson was told GSK, among other things, had been coding suicidal events as “emotional lability”.

Unbeknownst to either Farber or Jofre, GSK had submitted their application for the approval of Paxil for paediatric use a few weeks beforehand and FDA had a seven week deadline to respond. When on October 10th FDA sent an approvable letter to GSK they asked for further details on 12 items, including:

7/. [You] have listed paroxetine treated patients who experienced adverse events coded under the terms hostility, emotional lability or agitation. However the table did not include placebo patients nor did it include psychiatric adverse events that were coded under other terms. Please prepare an expanded version of this table including all psychiatric and behavioural adverse events and also those that occur among placebo patients. In addition it would be helpful if you could attach the narrative case summaries for those events that were either serious or resulted in premature discontinuation.

8/. Please provide your rationale for coding suicide attempts and other forms of self-injurious behaviour under the term emotional lability (FDA 2002).

Emails from the Edge

In response to the Secrets of Seroxat, Panorama had 65,000 calls and over 1,300 emails – the greatest response they have ever had to any program up to then. The responses were overwhelmingly congruent with what had been reported on the programme – that Paxil was linked to suicidality and dependence. Panorama had never repeated a topic before but ultimately did three more programmes on GSK and Paxil.

The response to the first program laid the basis for the second which aired on May 11th 2003 – Emails from the Edge (transcript from author). In this, Jofre again interviewed Alistair Benbow who on this occasion said that:

“The safety profile in children is very similar to that in adults with a couple of exceptions and we have provided that updated safety information to regulatory authorities around the world and specifically in relation to the potential for an increase in suicidal thoughts or suicidal attempts.

This increase is small. It is rather similar to, if you imagine a school of more than a thousand children, all of whom are deeply troubled by depression, less than a small class size would have these suicidal thoughts or attempts”.

The screening of Emails from the Edge led the leading patient advocate group for mental health issues in the United Kingdom, MIND, to protest outside the offices of the British equivalent of FDA, the Medical and Healthcare Devices Regulatory Agency (MHRA).

The MHRA announced a reactivation of an Expert Working Group that had been looking at the issues of suicide and dependence on SSRIs. This had been set up at the end of 2002, but had been disbanded because of undeclared conflicts of interest.

GSK were under sufficiently intense pressure leading up to Email from the Edge to produce glossy internal brochures and adverts internally for their own staff (Appendix 1), under the heading of “Science with a Conscience”.

At almost exactly the same time as this brochure was produced, in a letter dated May 22nd 2003 GSK wrote to FDA and other regulatory agencies around the world to update them on the new safety issues linked to children as Alistair Benbow two weeks earlier on Panorama had said they had already done.

The contents of this May 22nd letter were almost diametrically at odds with the brochure produced for internal company consumption. The internal material stated there was no compelling evidence linking Paxil to suicide. The submissions to FDA in contrast showed that Paxil doubled the rate of suicidal acts in children and did so in a statistically significant way compared to placebo. It showed an increased risk of suicidality during the active phase and 30-day taper phase in both Study 329 on its own and in GSK’s trials in children in general.

Where the internal GSK material had stated there was no evidence linking Paxil to violence, material presented to MHRAs working group around this time showed a doubling of violent acts on Paxil compared to placebo.

Where the internal GSK material denied any risk of addiction or dependence, the material presented to MHRA showed symptoms on stopping in a majority of healthy volunteers after exposures as short as two weeks.

Next Steps

On June 2nd 2003, 10 days after GSK's letter to FDA, Russell Katz of FDA sent an email to Andrew Mosholder one of the reviewers behind the dossier that led to the Paxil approvable letter (Full Email available on request).

Katz' email states:

“Andy – Hi, hope you are well.

We have recently become aware of a presumed association between paroxetine and suicidality in paediatric patients. We received a call from the EMEA little over a week ago. Dr Raines told us that the company (GSK) had submitted data that demonstrated that use of paroxetine in kids was associated with increased suicidality compared to placebo, and that the company proposed labelling changes. I believe she also said that it was in the news, and that it was a big issue. Tom and I told her that the company had not informed us of any of this and we agreed to look into it”.

This was ten days after GSK had sent Russell Katz their letter explaining exactly these points. As Katz's email hints, MHRA (for whom June Raine worked) were faced with patient groups protesting outside their building, and GSK were facing rebellious staff.

On June 10th MHRA acted. Paxil and other SSRIs were contra-indicated in children and adolescents.

GSK issued a series of Dear Doctor letters which made it clear that Paxil should not be given to children who are depressed and that there was an increased risk of problems linked to agitation and suicidality both on treatment and on withdrawal from treatment.

FDA issued an advisory noting concern about the prescribing of antidepressants in children.

Around this time, a tranche of GSK documents came into the possession of Panorama. These documents outlined GSK's marketing plans for Paxil during the 2001 and 2002 period aimed at making it the best selling antidepressant in the world. There were position papers detailing its strengths and weaknesses vis-a-vis other antidepressants. Some of these provided source material for Christopher Lane's book *Shyness* on the marketing of social anxiety disorder.

The key document however was billed as prepared by Julie Wilson designated as working for CMAAt-Neurosciences. There was a covering note by Jackie Westaway with distribution to senior marketing and medical personnel within GSK. The document had six pages. It was prepared in October 1998.

The document stated that the results of Study 329 were now available and did not show that paroxetine was effective for depressed children.

The document listed a number of strategic problems this posed for GSK and their proposed solutions.

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

“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”.

“It would be commercially unacceptable to include a statement that efficacy had not been demonstrated as this would undermine the profile of paroxetine”.

One of the proposed rescue measures was that:

“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 positive data were to become the Keller et al article.

The Genesis of a Scientific Fact

Facts neither simply appear nor appear simply in medicine. Despite the FDA advisory and despite FDA getting an analysis from GSK making it clear that Paxil caused adolescents to become suicidal and despite SSRIs being heavily discouraged in Europe, senior FDA officers began to downplay the risks of antidepressants.

On October 28th, the New York Times and Washington Post made it clear that FDA was less convinced there was a problem and were analysing the data prior to a full Pediatric Psychopharmacological Drugs Advisory Committee (PDAC) meeting scheduled for February 2nd 2004.

At the end of January 2004, ten days before the Psychopharmacologic Drugs Advisory Committee meeting to consider the issue of antidepressants and suicide, an American College of NeuroPsychopharmacology working group containing a number of those on the authorship line of 329 issued a position paper stating that there was no significant problem with antidepressants and suicide. This paper got widespread national coverage. Achieving widespread national coverage was part of the deal offered by GYMR, the public relations agency who had in fact written the paper for ACNP.

On February 1st, the San Francisco chronicle broke a story claiming that FDA's initial reviewer on the suicide issue, Andy Mosholder, had been gagged. Mosholder was the internal FDA reviewer whom Katz had approached in June 2003 to look into the issue of emotional lability in greater depth. He had then been charged with looking at the pediatric trial data. When he reported that there was a statistically significant doubling of the risk of suicidal acts on antidepressants, FDA would not allow him share his findings with FDA expert advisors at the February 2nd meeting.

At midday on February 2nd, the CMA-t document emerged into the public domain, at a press conference organized by Vera Sharav from the Alliance for Human Research Protection and Cindy Hall of the Baum Hedlund law firm.

GSK's immediate response to the CMA-t document was to claim that this was a document prepared by a consultancy agency that in no way reflected the position of the company, although the document claimed to be feeding back the opinions of GSK's marketing department.

GSK also made this claim even though the approvable letter from FDA in October 2002 had noted that:

“we agree that the results of Study 329 failed to demonstrate the efficacy of Paroxetine in paediatric patients with MDD. Given the fact that negative trials are frequently seen even for antidepressant drugs that we know are effective, we agree that it would not be useful to describe these negative trials in the labelling”.

At the February 2nd PDAC Bob Temple and Russell Katz denied that there had been any contact between MHRA or other regulatory agencies and FDA (Pers. Comm.). This position

seemed to involve equivocation at the time. Later, evidence such as Katz's email to Mosholder outlining his phone call with June Raine of MHRA came to light.

The advisory committee on February 2nd indicated that there were grounds for concern that antidepressants did cause some minors to become suicidal and little evidence that they worked.

In response, FDA opted to get a Columbia University working group to review all the behavioural events in these trials, to work out a rigorous classification system which would allow all parties to agree on the data to be excluded or not, with the resulting data to be considered at a follow-up PDAC meeting scheduled for September 14th 2004.

There was no obvious scientific basis for this manoeuvre. It looked like FDA was determined to resist efforts to have warnings

Meanwhile, the CMA-t document found its way on to the website of the Canadian Medical Association Journal. From there it came to the attention of Rose Firestein in the office of New York State's Attorney General, Elliott Spitzer. In June 2004, Spitzer's office initiated a fraud action against GlaxoSmithKline.

The resolution of this action two months later in August 2004 involved an agreement that GSK would post details of all their clinical trials on a website. It was this agreement that set the data access hare running.

As the September FDA hearings drew closer, another event shaped the story. A Congressional Action to investigate the gagging of Andy Mosholder reported by the San Francisco Chronicle in February had its first hearing on September 9th. Mosholder later testified that the data showed a problem but that officials higher in the system at FDA took a different view.

At the September 14th hearings, FDA presented data from Herschel Jick appearing to clear Paxil. These data were challenged by David Graham, another FDA whistleblower.

Data from the Treatment of Adolescent Depression Study (TADS) were produced, appearing to exonerate Prozac. But these data show a number of egregious distortions.

The committee ultimately voted in favour of an antidepressant-wide Black Box Warning for suicide. Russell Katz stated that FDA accepted that antidepressants cause suicidal behaviour.

Subsequently in April of 2006, GSK issued a Dear Doctor letter stating that there was a statistically significant increase in the risk of a suicidal act on Paxil in adults, and modified the Paxil label accordingly. But astonishingly FDA asked them to delete this which they did in August 2006. This was prior to a December 2006 hearing on antidepressants and suicide in adults that extended the Black Box Warning to 18-25 year olds.

To this day, a decade later, large numbers of US physicians appear to believe there is no evidence that antidepressants can cause suicide, and that FDA was simply bowing to some lobby like the Church of Scientology. There are continuing efforts to remove the Black Box warnings. These efforts involve collaborations between expert witnesses for the pharmaceutical companies and senior FDA officials.

329 & the Clinical Trial Literature

A great deal is now known about the publication of the Keller article.

The true author is not listed on the authorship line. It was in fact Sally Laden, then working for Scientific Therapeutic Information (STI), a company specialized in ghostwriting scientific manuscripts. Laden's point person within GSK was James McCafferty.

On July 19th 1999 McCafferty emailed Laden. Under a "safety" subheading he wrote:

"It seems incongruous that we state that Paroxetine is safe. I know the investigators have not raised an issue.... I am still not sure how to describe these events. I will again review all the events to make myself feel comfortable about what we report in print".

Despite the fact that the company did not regard the trial as having proven the drug was either effective or safe the material prepared by GSK's PR Agency Cohn and Wolfe given to the sales representatives as of August 2001 stated:

"this 'cutting edge' landmark study is the first to compare the efficacy of an SSRI and TCA with placebo in the treatment of a major depression in adolescents. Paroxetine demonstrates REMARKABLE efficacy and safety in the treatment of adolescent depression".

Study 329 is not an anomaly. This is common with pharmaceutical company publications. As of 2004 the entire clinical trial literature on SSRI's in children was either company written or ghost written.

Despite huge fines and a fraud case against GSK, the Journal (JAACAP) has refused to retract the article and the company continues to stand behind its article.

As of 2004, the publications stated universally that SSRIs were effective and safe for children while the actual raw data when they came to light made it clear that none of the trials had shown that any of the treatments worked or were safe.

There is overwhelming evidence that the adult antidepressant literature has been cut from exactly the same cloth as 329. Indeed the literature on the majority of on-patent drugs with blockbuster potential is likely to be similar.

While the literature on drug treatment was becoming ghost-written and often completely at odds with the underlying data, there was a related development in academic publishing. It became increasingly difficult to publish any articles showing that paroxetine or other drugs can cause adverse events. The BMJ, the Lancet, the New England Journal of Medicine, the Journal of Medical Ethics and a range of other publications were increasingly likely to turn down publications on the basis that they were concerned that a legal action taken by a pharmaceutical company might put them out of business.

One of the best symbols of the newly emerging situation was an effort to get an article on Study 329 published in Index on Censorship. This journal, although conceding that it was in receipt of documentation that supported every point being made in an article quite like this one about Study 329 opted to self-censor.

Study 329 & Access to Trial Data

The CMA-t document led to a fraud action against GSK in 2004. The resolution of this action involved an agreement that GSK would post details of all their clinical trials on a company website.

This commitment led to the publication of the first Clinical Study Reports (CSRs) made publicly available. These were for the trials of Paxil done in children. The Keller article was 10 pages long. The CSR for 329 was 782 pages long.

The summary reports of many trials in other therapeutic areas, including trials of rosiglitazone (Avandia) were also made available. These summaries were 3-7 page documents.

Reviewing the Avandia summary reports, Steven Nissen from the Cleveland Clinic compiled data on the rates of mortality on Avandia and placebo in Avandia trials. These demonstrated an increased rate of mortality and led to Avandia being withdrawn from the European market and restricted in the US.

In July 2012, GSK agreed to plead guilty to criminal charges and pay the US government \$3 Billion for promoting its antidepressants for unapproved uses and failing to report safety data about Avandia.

Company Offers of Access to Clinical Trial Data

In 2010, following an initiative from Peter Gotszche, the European Ombudsman ruled that there should be open access to clinical trial data held by the European Medicines Agency (EMA).

The pharmaceutical companies swung into action in an attempt to manage the process. Following a hearing at EMA in London in November 2012, GSK put out a press release saying that they were going to throw open access to their clinical trial data.

Andrew Witty, the CEO of GSK, also embraced an AllTrials campaign to register all clinical trials, leading transparency campaigners to laud the company. The BMJ featured Witty on the front cover of the March 9th 2013 issue of the journal billed as the acceptable face of Big Pharma (BMJ 2013).

At the same time another company AbbVie launched a legal action against EMA, blocking access to all clinical trial data.

Although for a considerable period during 2013, GSK and AbbVie were portrayed as the apparent good and bad guys of the pharmaceutical industry, in fact both companies proposed the same thing – a “responsible” method of accessing a limited range of company data. Both asserted Corporate Privacy Rights. Both argued that access had to be restricted to ensure that patient confidentiality was not compromised.

Accessing the Data from Study 329

In July 2012, Peter Doshi of the Cochrane Tamiflu group noted that the CSRs for the pediatric antidepressant trials posted by GSK on the company website, including that for Study 329, did not come with the appendices noted in the body of the CSRs. He wrote to New York State’s Attorney General’s Office about this (Pers. Comm.).

This led GSK to add the appendices. In the case of Study 329, this mean adding appendices A-G, but GSK were not prepared to add appendix H. Appendices A-G contain the protocol and summary tables of the data from 329. These come to 5,494 pages. Appendix H contains the Clinical Record Forms (CRFs) which come closer to the actual data. This has approximately 77,000 pages.

In June 2013, Doshi and colleagues proposed a new initiative to Restore Invisible and Abandoned Trials (RIAT) (Doshi et al 2013). The first study that any academic group has taken on to restore has been Study 329.

This has involved applying to GSK for access to the data. GSK have offered the re-authors access through a remote desktop without the ability to download the data (Appendix H). This makes the operation cumbersome and almost certainly limits the capacity of any investigators to spot patterns in the data.

When published the re-authored study will come with appendices A-G attached. It is likely to differ from the Keller et al paper on issues of efficacy and adverse event profiles. It will mark the first time in the academic literature where there are two radically different published interpretations of a study's data. It remains to be seen whether the availability of the data in the case of the one of the versions will have an effect on how the two articles are viewed.

Continuing Restrictions on Access to Data

It is clear from the above that despite trumpeting transparency, GSK continue to block access in usable form to the data from their studies. One of the two major blocks to access to the data that companies, including GSK, offer is the risk to patient confidentiality. This is billed as a concern for the patients who have enrolled in trials.

But in Study 329, the consent form states:

“Treatment with imipramine could produce side effects. The most common are dry mouth, blurred vision, rashes, nausea, changes in heart rate, fainting, restlessness and agitation. I understand that I am not more likely to experience side effects as a result of my participation in this study than if I were being treated with paroxetine or imipramine in the usual manner”.

In fact, the commonest adult dose of imipramine is 150mg, and lower doses are often used. The children in Study 329 were all to be treated with a minimum of 150mg of imipramine and then titrated up to 300mg in all cases if possible.

This trial design looks like an effort to make imipramine look bad and paroxetine relatively good by contrast. There was a predictably high drop-out rate on imipramine, predictably for cardiovascular problems, consistent with this interpretation (Data in preparation).

GSK later revealed there was a statistically significant doubling of the rate of suicidality on paroxetine compared to placebo in this study. It is possible that any children in whom suicidality was induced have been put at an increased risk of becoming suicidal in the future. They also are far more likely to have poor responses to other SSRIs. It is important for their self-image and future clinical care that they are made aware of the possible role of paroxetine in triggering these events.

In normal clinical practice it would be appropriate to warn the patient that the suicidality they had just experienced was possibly linked to treatment so that they can avoid this drug or drugs from this group in the future. It would also be normal to explain to patients with cardiovascular problems on imipramine what had happened to them.

GlaxoSmithKline have made it clear they have made no overtures to any of those affected. They have invoked the learned intermediary doctrine that it is down to the doctors of those affected or the institutions from which the trial was run to look after the children recruited.

Unless there is an outreach to patients injured in clinical trials, it is difficult to believe that any companies' proposals about responsible access to clinical trial data and protecting patient confidentiality are based in a concern for patient welfare rather than other concerns.

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BMJ March 9th 2013. GSK's Andrew Witty. The acceptable face of Big Pharma?

Appendix

The Cover:

Were the UK doctors who wrote 4,580,000 prescriptions for Seroxat last year right?

Inside there were pages of text with facing pages on which there was a Strapline.

Page1:

Seroxat has helped tens of millions of people lead fuller and more productive lives.

At GlaxoSmithKline we believe that the best people for patients to consult about their treatment are their own doctors. Who knows more about the background of each individual patient and the appropriate treatment for different conditions?

Unlike TV reporters doctors are aware of the huge advances that have been made in the treatment of depression in the last few years. Seroxat is an SSRI, a breakthrough in the treatment of depression and anxiety.

As a class, SSRI's are probably some of the most extensively investigated medicines available in the UK today.

Their safety is constantly monitored by the Medicines and Healthcare Products Regulatory Agency (MHRA) – a rather more expert body than the producers of Panorama.

Strapline 1:

If you are depressed who should you consult? A TV presenter or a doctor?

Page 2:

Seroxat is an effective treatment with a well established safety profile and a wealth of positive experience involving thousands of doctors, tens of millions of patients and over ten years experience worldwide since its UK launch in 1991.

Seroxat is not addictive.

Seroxat prevents suicide by treating depression and helping to reduce suicidal thoughts.

The majority of patients do not get side effects on either taking Seroxat or stopping.

We have total faith in Seroxat so can you.

By 2020 the World Health Organisation estimates that depression will be the second most burdensome illness worldwide. Depression is a potentially deadly disease that affects a huge number of people in the UK.

At any one time 1 in 7 people are affected by depression. Worst still 1 in 7 people with depression commit suicide. Every year this results in the death of 3,000 people in the UK with devastating consequences for their friends and family.

However there is good news. As antidepressant usage has increased suicide rates have fallen at 15% during the 1990's.

Strapline 2:

Depression affects 5million people in the UK. Seroxat is a highly effective answer.

Page 3:

Contrary to the claims of the Panorama programme:

In clinical trials of over 9,000 patients treated with Seroxat, the majority of the reporting symptoms on stopping were short lived, mild to moderate in intensity and the majority resolved on their own within two weeks.

There is no compelling evidence that Seroxat is linked to an increased risk of suicide.

Data shows that Seroxat will reduce violence and aggression and help prevent self harm.

We take every single report seriously. No treatment is perfect for every individual patient and it is up the doctor to decide in conjunction with the patient exactly what treatment is best for them.

And bear in mind in clinical trials, 60% of patients who took the placebo experienced side effects that they thought were related to the treatment.

Strapline 3:

Judge Seroxat on clinical trials not trial by media.