

Secrets of the drug trials

Panorama

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**INTRODUCTION:**

**Secret emails reveal that the UK's biggest drug company distorted trial results of an anti-depressant, covering up a link with suicide in teenagers.**

Panorama reveals that GlaxoSmithKline (GSK) attempted to show that Seroxat worked for depressed children despite failed clinical trials.

And that GSK-employed ghostwriters influenced 'independent' academics.

GSK told Panorama: "GSK utterly rejects any suggestion that it has improperly withheld drug trial information."

GSK faces action in the US where bereaved families have joined together to sue the company.

As a result, GSK has been forced to open its confidential internal archive.

Karen Barth Menzies is a partner in one of the firms representing many of the families.

She has examined thousands of the documents which are stored, box upon box, in an apartment in Malibu, California.

She said: "Even when they have negative studies that show that this drug Seroxat is going to harm some kids they still spin that study as remarkably effective and safe for children."

GSK's biggest clinical trial of Seroxat on children was held in the US in the 1990s and called Study 329.

Child psychiatrist Dr Neal Ryan of the University of Pittsburgh was paid by GSK as a co-author of Study 329.

In 2002 he also gave a talk on childhood depression at a medical conference sponsored by GSK.

He said that Seroxat could be a suitable treatment for children and later told Panorama reporter Shelley Jofre that it probably lowered rather than raised suicide rates.

In amongst the archive of emails in Malibu, Shelley was surprised to find that her own emails to Dr Ryan from 2002 asking questions about the safety of Seroxat had been forwarded to GSK asking for advice on how to respond to her.

She also found an email from a public relations executive working for GSK which said: "Originally we had planned to do extensive media relations surrounding this study until we actually viewed the results.

"Essentially the study did not really show it was effective in treating adolescent depression, which is not something we want to publicise."

But the article was published in the Journal of the American Academy of Child and Adolescent Psychiatry which says it ranks as number one in child mental health in the world.

The editor in chief of the British Medical Journal, Fiona Godlee, said that what she calls the "blind-eye culture of medicine" should be exposed by professionals.

She has written in response to the Panorama film: "We shouldn't have to rely on investigative journalists to ask the difficult questions.

"Reputations for sale are reputations at risk. We need to make that risk so high it's not worth taking."

The Medicine and Healthcare Products Regulatory Authority (MHRA) began a criminal investigation into GSK three years ago but no action has been taken yet.

A spokesperson told Panorama that the investigation has been given substantial additional resources and remains a high priority.

Seroxat was banned for under 18s in 2003 after the MHRA, revealed that GSK's own studies showed the drug actually trebles the risk of suicidal thoughts and behaviour in depressed children.

**Secrets of the Drug Trials Monday 29 January at 2030 on BBC One and this site.**

#### **TRANSCRIPT:**

JEREMY VINE: Hello, I'm Jeremy Vine and this is Panorama. The secret emails you weren't supposed to see. The paper trail that reveals how results of drug trials were glossed over to cover up a link with suicide in teenagers. Now GlaxoSmithKline faces trial for fraud.

When you take your child to the doctor you assume the medicine they are prescribed is safe and will help them get better. If your teenager is depressed, you certainly don't expect the drug they're given to make them want to kill themselves. But we've uncovered the story of how one company tried to hide the fact that it's medicine did exactly that. Just watch this.

Reporter: SHELLEY JOFRE

Malibu, California. It's not where you'd expect to unravel one of the biggest medical scandals of recent times, but that's exactly what this team of lawyers has managed to do. What they've found affects all of us here in the UK, anyone in fact who takes prescription medicine.

KAREN BARTH MENZIES

Lawyer, Baum Hedlund

It is all about the profits. Even when they have negative studies that show that this drug is going to harm kids they still spin that study as: "remarkably effective and safe for children."

JOFRE: This apartment is crammed full of boxes containing a story that Britain's richest drug company has fought hard to suppress. There's an embarrassment of secrets here that GlaxoSmithKline really doesn't want you to see, and you're about to discover why.

So it's all stuff from the confidential GlaxoSmithKline archives?

BARTH MENZIES: Yeah, the internal documents, the emails back and forth, the decisions that they make from the bottom to the top.

SHELLEY JOFRE

These trade secrets are usually protected by law but through a series of legal challenges the lawyers have forced many of them into the open. Buried in all these boxes are details about secret clinical trials programme that GlaxoSmithKline began over a decade ago for its antidepressant Paroxatine, it's a drug that's better known in Britain by its brand name Seroxat. It was hailed in the 90s as a wonder drug when it was launched as a rival to Prozac to treat depression and anxiety. GSK later promoted it as a cure for everything from stress to shyness. By the new millennium 100 million Seroxat prescriptions have been written worldwide bringing in 2 billion dollars a year. With the adult market also all sewn up, the company then looked for new ways to make money out of Seroxat.

BARTH MENZIES: If they tested Seroxat for children they would get a six month extension on their patent which means enormous profits. It would become the antidepressant, being used worldwide for children in depression.

JOFRE: The documents in these boxes reveal how hundreds of children with depression were recruited from around the world to take part in three large scale clinical trials of Seroxat. The biggest of these was in the US and came to be known as 'Study 329'. Its influence would reach right across the Atlantic to British doctors looking for ways to treat depressed children.

STEPHANIE: She painted this when she was 16.

JOFRE: And this is Sharise.

STEPHANIE: That is Sharise and I just love that painting.

JOFRE: Six years ago Stephanie Gatchell took her daughter Sharise for a hospital appointment in Northamptonshire. Sharise hadn't yet started her periods and was worried about it.

STEPHANIE GATCHELL

During that consultation she became a bit emotional. I was amazed, she started crying, and he... I clearly

remember him asking her: "Sharise, do you sometimes feel like ending it all?" I couldn't believe it when she said: "Yes, I do." And then he started talking about Seroxat and suggesting that she try that.

JOFRE: Seroxat was only licensed for adults but doctors can prescribe any medicine if they think it will help their patient. It's called: 'off-label prescribing' and Sharise wasn't the only teenager getting Seroxat off-label. Around 7000 children a year were on the drug in Britain alone. Within days of starting on Seroxat Stephanie noticed a dramatic change in her daughter. She became more confident but with it came aggression and worse.

STEPHANIE: One day in the kitchen her sleeve pulled up slightly and I noticed that she... there were cut marks on her left arm. God! I couldn't believe my eyes. She was obviously self-harming while she was on Seroxat, something she'd never ever done before.

JOFRE: Stephanie persuaded her daughter to stop taking Seroxat but in 2003 Sharise went back on the drug without telling her mum. Her parents went away for the weekend, not realising she was taking Seroxat again.

STEPHANIE: The moment I walked into the house I knew something was wrong. I ran upstairs before my husband came in, and the moment I got to the landing at the top... (Steph breaks down, crying) ... she was hanging... she was hanging from the loft hatch. I tried to revive her but I... before I even started I realised I was too late. I could see that. I could see it was too late, but she was still warm.

JOFRE: Next to her daughter's suicide note lay a packet of Seroxat. She instinctively blamed the drug, but she couldn't have known what its maker knew. The company had tested the drug on depressed children six years previously. One group took the drug, the other a placebo - sugar pills. The results were unexpected: Seroxat proved no better than the placebo. In one study seven of the 93 children who took Seroxat had to be taken to hospital. Some had self-harmed like Sharise.

BARTH MENZIES

Baum Hedlund

It should have been the time where they at least by then started warning physicians who prescribing this drug off label to stop prescribing it to children, because not only is it not effective, it's not safe.

Reconstruction

JOFRE: There's no doubt the company knew it had a problem. The product director for Seroxat in the UK admitted as much in an internal memo to senior executives way back in 1998. It's one of dozens of emails and memos seen by Panorama.

Email dated: 14th October 1998

"The results of the studies were disappointing. The possibility of obtaining a safety statement from this data was considered but rejected."

JOFRE: In other words they knew they wouldn't get a children's licence.

[Email] "The best which could have been achieved was a statement that although safety data was reassuring, efficacy had not been demonstrated."

JOFRE: They hadn't even shown that the drug worked.

[Email] "Consultation of the marketing teams confirmed that this would be unacceptable commercially.

JOFRE: Publishing the data in full would put profits at risk. But if they couldn't get a children's licence, could they find an unofficial way to market Seroxat for childhood depression? Exit the doctors - enter the spin doctors. They would help create a new story. Seroxat was safe and it did work for teenagers. The inconvenient facts would be buried and the marketing people would spread the good news to doctors around the world. Every stage in this clinical process is contained within these boxes.

BARTH MENZIES: They figured out ways that they could downplay the risks, blow up out of proportion the supposed benefits or the good sides of the study and really downplay the negative findings.

JOFRE: The next step was to use apparently independent academics to help, like Professor Martin Keller. Head of Psychiatry at a prestigious university his name is worth a lot to companies like GSK.

BARTH MENZIES: They figured out well if we use opinion users in the field, academics that everybody looks up to and the leaders in the field to sell our product, doctors are going to be far more influenced than by just regular sales representatives.

JOFRE: So just what quality should a key opinion leader possess. Here's professor Keller in his own words giving video evidence to lawyers who are suing GlaxoSmithKline.

Professor MARTIN KELLER

Brown University

You're respected for being a.... um... how to put this, an honourable person, and therefore when you give an opinion about something, people tend to listen and say oh, this individual gave their opinion, it's worth considering.

JOFRE: But how independent is he? In a single year Martin Keller earned half a million dollars from drug companies including GSK. His name is at the head of GSK's study 329 but how much input did he really have? In a memo Dr Keller thanked a ghost writer for the initial preparation of the manuscript, a ghost writer who works for a PR company - a PR company hired by GSK.

"You did a superb job with this. Thank you very much. It is excellent. Enclosed are some rather minor changes from me..."

JOFRE: Here's another letter from the ghost writer to Dr Keller. It says that all the necessary materials are enclosed so that he can submit study 329 for publication, even down to the covering letter which says: "please re-type on your letterhead. Revise if you wish." Ghost-written medical research like this is becoming a real problem.

Dr FIONA GODLEE

Editor, British Medical Journal

If the people who originally designed the study collected the data and analysed the data aren't involved in actually getting right through to the interpretation there are all sorts of slips and manipulations that can happen at that stage which I think have to be against the public interest.

JOFRE: So just how closely did the honourable Professor Keller scrutinise the data in his own study?

PROF KELLER: I've reviewed data analytic tables, I don't recall how raw it was. The huge printouts that list items by item number.. you know, item numbers, invariable numbers and don't even have words on 'em. I tend not to look at those. I do better with words than I do with symbols.

JOFRE: A telling phrase. And it's soon clear the PR woman is making crucial decisions about how to present the data. At one point a GSK executive protests: "She's going too far in burying bad news."

It seems incongruous that we state it as safe yet report so many serious adverse events. [email dated: 19th July 1999]

JOFRE: There were actually 11 such side-effects including self-harm, aggression and suicidal thoughts. GSK suggests to the PR woman that she make clear Seroxat may have caused all of them. But how's this for spin? The final article says:

"Of the 11 patients only headache (one patient) was considered to be related to the treatment."

JOFRE: The article never does explain how many children became suicidal or explore whether the drug was to blame. Instead it concludes that Seroxat is "generally well tolerated and effective." The next step in GSK's marketing plan was to get the study published. Doctors rely on medical journals to give them advice they can trust. The first journal GSK tried rejected the article, so they tried another.

Dr MINA DULCAN

Editor, Journal of the American Academy of Child & Adolescent Psychiatry

We rank, and this is a worldwide ranking, we rank number one in child mental health and number two in paediatrics.

JOFRE: About as influential as GSK could hope for, but would the journal's reviewers spot the flaws in the study? Normally their deliberations are confidential but we've seen what they thought of study 329.

"Overall results do not clearly indicate efficacy. Authors need to clearly note this." [3rd November 2000]

JOFRE: Another points out:

"A relatively high rate of serious adverse effects was not addressed in the discussion."

JOFRE: And fundamentally poses the question:

"Given the high placebo response rate, are these drugs an acceptable first line therapy for depressed teenagers?"

GODLEE: I think it's fair to say that what happened here is one journal spotted the problems and rejected the paper. Another journal had peer reviewers who also spotted a number of the problems but the paper was published nonetheless relatively unchanged, and I think the journal must take some responsibility for that.

JOFRE: Do you have no regrets about publishing this study?

DULCAN: Oh I don't have any regrets about publishing at all. It generated all sorts of useful discussion which is the purpose of a scholarly journal.

JOFRE: Inside GSK, though, the discussion was all about what a failure study 329 had been. This is what another of its PR people wrote when asked if the journal article would be publicised.

"Originally we had planned to do extensive media relations surrounding this study until we actually viewed the results. Essentially the study did not really show it was effective in treating adolescent depression which is not something we want to publicise." [Email dated: 5th March 2001]

JOFRE: The same month the journal article was published, the third of the company's clinical trials in depressed children reported back. Would this one back up the company's public claims for Seroxat? Not at all. It actually showed the children on Seroxat did worse than the ones on sugar pills. Yet doctors at this time asking GSK for advice on treating children were told that study 329 showed the drug..... "was superior to placebo by several assessment methods." No mention of the serious side-effects or the two failed studies. Meanwhile GSK was telling its American sales reps who promote drugs direct to doctors that Seroxat: "demonstrates REMARKABLE efficacy and safety in the treatment of adolescent depression."

STEPHANIE GATCHELL: They have been deceiving the world... the population, the doctors, everybody, and I think they've... what they've done is just despicable. I'm very, very angry. It's an anger I don't often know what to do with.

KAREN BARTH MENZIES

Baum Hedlund

They didn't tell the regulators or the physicians or parents about these risks or the lack of efficacy, instead they went out and promoted this specific study as remarkably effective and safe for kids.

JOFRE: So what does that amount to in your view?

BARTH MENZIES: That's a lie. That's flawed.

JOFRE: This was a drug that doctors were told could help prevent suicide when in reality it was actually making some children suicidal, a triumph of marketing over science. Nearly five years ago I started asking questions about Seroxat's safety in children, after reports of worrying side-effects in adults. So did GSK and its supporters come clean about what they knew or continue to cover up the truth? Back in 2002 I interviewed another academic paid by GSK to work on study 329. Doctor Neil Ryan is an eminent child psychiatrist. He was speaking at an American medical conference sponsored by..... yes,

GlaxoSmithKline. Dr Ryan told an audience that included British doctors Seroxat was effective for a child who had depression. He didn't mention the small issue of suicide. So afterwards I asked him about it.

Dr NEAL RYAN

University of Pittsburgh

It looks like in fact that the antidepressants overall lower the rate of suicide rather than raise it. It's been a question that's really important because it's such an awful outcome you can't treat people that are dead, you know, but it's looking like it's not the case.

JOFRE: I wondered even then how he could be so sure. Back in Britain I called him.

13th September 2002

I'm trying to find some more information about it from you because I know you were one of the main authors and I think you had access to all the data so...

RYAN: Yes, I've given you all I can give you Shelley. Good luck with your story.

JOFRE: You can't tell me whether the children were self-harming or trying to kill themselves?

RYAN: [No response]

JOFRE: Hello? Hung up again. Fast forward four years and the boxes in Malibu reveal what was going on behind the scenes. This, supposedly independent academic was asking the company that sponsored his research how to respond to me.

BARTH MENZIES: If you look here he emails all of your correspondence to GlaxoSmithKline.

JOFRE: [reading from file] "I'll call you again later today and you can advise on how might be best to handle this." Who's.... that's somebody from GlaxoSmithKline so he's forwarded all my emails to them and asked for advice.

BARTH MENZIES: Yeah, you see they are truly... these academics are truly spokespersons for the drug company.

JOFRE: Back in 2003 I eventually spoke to a senior GSK executive and despite what the company was admitting internally, the message for the outside world was that study 329 was absolutely sound.

The evidence here suggests that their children might be at more of suicide if they go on Seroxat.

October 2002

Dr ALISTAIR BENBOW

GlaxoSmithKline

No, the evidence is not there. There is no statistical difference between the groups. The reality of the situation is that in this trial Seroxat was generally well tolerated by this difficult to treat population.



JOFRE: That simply wasn't true. After the programme a staggering 67,000 people contacted us with their own Seroxat stories.

I did attempt suicide a couple of times.

I just put the point to my arms and just scrape until it bled.

I would cut myself with razors.

I did just want to die.

JOFRE: I kept pursuing this story but six months later Dr Benbow still wouldn't budge.

BENBOW: These medicines are not linked with suicide. These medicines are not linked with an increased rate of self-harm.

JOFRE: Professor David Healy is an academic who has long challenged the company line. He's angry that doctors were deceived into prescribing a harmful drug to children.

DAVID HEALY: If you'd heard the experts talk, they all say the drug was extremely safe and very effective. We were all hoodwinked, misled, duped. They produce these clinical trials which appear to be evidence and they aren't, they're adverts.

JOFRE: Sharise Gatchell's doctor, like thousands of others, prescribed Seroxat in good faith.

STEPHANIE GATCHELL

Sharise was prescribed Seroxat on the 7th May 2003. On the 11th the Panorama programme was broadcast. We watched it together. We called her and said: "Come and look. Look, Seroxat, you see, you shouldn't have been on it. Aren't we lucky that you're off it." We didn't realise she was taking it secretly again.

JOFRE: The following month some dramatic news.

10th June 2003

[NEWS]

Government's drug safety advisers have warned that the antidepressant drug Seroxat shouldn't be given to anyone under 18 years old.

JOFRE: The reason: Seroxat trebles the risk of suicidal thoughts and behaviour in depressed children. The medicines regulator had worked this out from the secret clinical trial data GSK had finally handed over - 2 years after the last depression study had ended. But it didn't come in time for Sharise Gatchell.

STEPHANIE: I couldn't believe it! I couldn't believe it, two weeks after she died. Why not just three weeks earlier or four weeks earlier, we wouldn't have had that problem. Everything came too late for Sharise.

JOFRE: GlaxoSmithKline didn't want to be interviewed but told us the company utterly rejects any suggestion it has improperly withheld drug trial information and points out that Seroxat has never been approved for under 18s. GSK rightly says that no suicides were reported in the children's studies, and claims none of the individual trials were considered by GSK or independent investigators to show a clinically meaningful increase in the rate of suicidal thinking or attempted suicide.

A copy of the full statement is available on our website [bbc.co.uk/panorama](http://bbc.co.uk/panorama)

But the boxes in Malibu reveal that the company did find a clinically meaningful increase in 2004 when forced by the US medicines regulator to go back through its own trial results. Miraculously they discovered a further four children on Seroxat who had become suicidal during study 329.

KAREN BARTH MENZIES

Baum Hedlund

They discovered that there was actually a six fold increase in events relating to suicide.

JOFRE: But how could all of this be missed originally? I mean these people were academics, they were supposed to be objective and they were supposed to be scrutinising the data!

BARTH MENZIES: It shows that they didn't.

JOFRE: In an email exchange I've seen, the supposedly independent investigators seem surprised by this news. Dr Ryan tells professor Keller that: "Unfortunately the extra suicidal cases were all on Seroxat, or Paxil as it's known in the States." Dr Ryan was recently asked about this while giving video evidence.

Q: Did you go back and correct your paper?

RYAN: The... the GSK was getting the data out there so it wasn't... there was no erratum to the paper. This was a subsequent analysis.

Q: So no erratum to your paper has been done to your knowledge.

RYAN: To my knowledge not.

JOFRE: Toronto last summer, 15,000 psychiatrists from Britain and around the world are here for the profession's largest annual conference. The whole event is sponsored by the big drug companies. Martin Keller, the key opinion leader, is here doing what he does best, influencing medical opinion. We weren't allowed to film his speech so wired with a secret camera I caught up with him afterwards to ask if he was worried about the high number of suicide attempts on study 329.

Secret filming

KELLER: None of these attempts led to suicide and very few of them led to hospitalization. The thing is, you have to consider what are the alternatives. Right.

JOFRE: So some of the unpublished studies showed that placebo actually seemed to have more of an effect.

KELLER: Come on, you know better than that.

JOFRE: Hang on, rewind a second. Yeah, he really did just stroke me under the chin.

So you still stand by.. you're still.. you'd be quite happy to still prescribe..

KELLER: Absolutely. I think..... [averting gaze] yeah.

Professor DAVID HEALY

University of Cardiff

We're in a situation now where people who are ill generally have been deeply betrayed by the whole process, deeply betrayed by the pharmaceutical companies and by all the experts that have been willing to actually lend their names to the process.

JOFRE: Do you think what happened with study 329 actually matters in a broader context?

Dr FIONA GODLEE

Editor, British Medical Journal

I think what it tells us is that we do have a problem. We know that it's not the only case and we have to work very hard not only to uncover cases such as this but to work out how to prevent things like this happening in the future.

JOFRE: This scandal shows just how tightly the drug companies control medical research. In the US bereaved families have joined together to sue GSK claiming it acted fraudulently.

[STEINBERG v. GSK]

[V/O pictures of victims] The case should come to court later this year and if it succeeds the company could be forced to pay out millions of dollars to the families.

BARTH MENZIES: This is Scott, 14 years old. This is a little boy who's 11 years old. He started taking Seroxat and he ended up.. he hanged himself in the closet with the leash of his new pet puppy.

JOFRE: Stephanie Gatchell and her husband have moved away from the home that holds so many awful memories to try to start a new life in Ireland, but they just can't forgive GSK for concealing what it new about Seroxat.

STEPHANIE: They just kept on denying and denying and denying. A programme like Panorama virtually had to force them to admit. When were they... were they ever going to come out with the truth on their own? I don't think so. The decision makers in that company should... you know, should be brought to justice. They have a lot to explain.

JEREMY VINE: Shelley Jofre reporting. Now following revelations on this by Panorama 3 years ago the medicines regulator here did begin a criminal investigation but as yet no action has been taken. A spokesman said the investigation is still high priority and now has substantial extra resources.