Study 329 Talk

Professor David Healy, Lyon, UCBL1, October the 15th, 2019

October 10th is World Mental Health Day and 3 days before October 10th, in 2002, the front cover of Newsweek in the United States featured this teenage girl and it told parents over in the United States that teenagers were quite likely to get depressed. And if this wasn't treated, they would go on to a life of alcoholism and drug abuse and divorce and job failure and suicide. But there was good news, we now had new treatments for teenagers who were depressed. Prozac had just been approved for use in this age group and as Newsweek knew, Paroxetine, called Paxil in the United States, and Zoloft were just about to be approved by FDA.

So, a year before, a clinical trial of Paxil in children who were depressed which had been carried out in the United States had just been published in the journal with the highest impact factor in child mental health. And it had an authorship line to die for: these were very big names in the field. So, these authors' names were on the article and it was in this journal: this was something that most doctors were going to believe. This was study 329. Now, it is often called the Keller and al. article after its first author's name, Martin Keller. The trial, the protocol for the trial had been brought up ten years previously. The trial had begun 8 years previously and it had concluded three years before the published article came out. So it took three years from the point the trial ended to the point of publication of this article which said this drug works wonderfully well for teenagers who are depressed and it's safe, there are no problems giving it.

The sales representatives for the company were told by the marketing department that « *this is the kind of thing you say to doctors: this is a cutting edge, landmark study which shows SSRIs, our SSRI is very helpful for teenagers who are depressed, much better than the older antidepressants we had* ».

So, now, at that point in time, this is at 2002, any of you who are involved in medicine and went on to mental health meetings or cardiology meetings or internal medicine meetings in the United States at least and in Europe also, this was the scene you saw. Yes, there were lectures happening in lecture theatres, but a huge area in the conference was occupied by the pharmaceutical companies selling their drugs . And this is Philadelphia in 2002, just before Mental Health Day,

and on the program for the meeting, there were reports from three clinical trials of Paxil being given to teenagers who were depressed or teenagers who were anxious or teenagers who had various different problems.

And all of these abstracts, and to most doctors at the meeting, these would appear as totally separate clinical trials.

So you got three different clinical trials and all making the same claim: out drug is great for teenagers and it's very safe to give.

And in and around that time, Glaxo-Smithkline who make Paroxetine were willing advertising a (…) for helping persuade people who are shy and introvert that they have an illness called « social anxiety disorder » and you'd be held back by this illness. If you just take our treatment, you're going to be able to succeed in life, you're going to be the person you really want to be. And these adverts won awards for being so good and the upshot for this was the company, at this point in time, Paxil was earning, for the company, 2 billion per year, which, back then, was a very large amount of money.

So, three days before Mental Health Day, Newsweek was letting people know we've got good treatments for children who were depressed and Prozac had been approved. And three days after the Newsweek article, as Newsweek knew, this is FDA writing to GlaxoSmithkline saying « *we are*

happy to approve Paroxetine for teenagers who are depressed ». Very few people will have seen this letter from FDA, this isn't the kind of document that's out there anywhere that you can find easily. But there was a problem looming that GSK did know about and FDA didn't know about. It was what we can call the « little girl says the Emperor has no clothes problem ».

This is Shelley Joffre. And she is not trained in medicine and she is not trained in science. She's a journalist. And she's part of a BBC team who work for a program called Panorama

which is one BBC investigative affairs programs. And until this issue, Panorama in 50 years had covered lots of topics that had never repeated themselves. On this topic, Panorama made four programs.

For the first program, their interest began because, first of all, GlaxoSmithkline, GSK for short, were a UK company and they had become the largest pharmaceutical in the world and were headquartered just down the road from the BBC, so it seemed an obvious idea to make a program. The other thing was their drug had just become one of the best selling drug in the world and it had also, in 2001, ended up in the wrong side of a verdict for the first time. This was the Tobin trial where Don Shell whom you see on the left there had been given Paxil by his family doctor for sleep problems. And 48 hours later, Don Shell put three bullets to the head of his wife, Lisa, whom you see, he's holding her waist here, and three bullets to the head of his daughter and three bullets through the head of his grand-daughter whom you see in this daughter's arms before killing himself. And the jury in Cheyenne, Wyoming, returned a verdict against GSK and this is the first verdict ever been returned against a pharmaceutical company for a behavioural problem their drug had caused. So, this was of interest to the BBC. The case is called the Tobin case because the only person who didn't get killed here in the picture was the man on the far right who was the daughter's husband.

So, the BBC found to go to Philadelphia at the American Psychiatric Association meeting to interview the authors of study 329 who are here, most of whom were going to be at that meeting. And the producer of the program gave Shelley Joffre study 329 to read on the plane on the way. This is the first time she has seen it. As I said she didn't have the background training on these that probably all of you here in this room have. And that meant, maybe, that it was easier for her to spot the problems that most of you and most of us missed. The idea behind the program first of all was that this trial had been done on children who were poor from deprived parts of the United States and they really needed to find out what the background story was. But when she read the article, she was interested by the idea that a lot of children had become « emotionally labile » in this trial. « *What does « emotionally labile » means?* », she asked. She was told « *pay no heed to that, we're interested in just where the clinical centres for this trial were and why they were recruiting poor black children from deprived neighbourhoods.* » So when she got to interview the authors, none of them agreed that any of the children were from poor deprived areas. But when she asked any of the authors just to explain what « emotionally labile » meant, they all began to look very nervous and she became more and more convinced that there was something important about this term.

This just gives you an email exchange between herself and one of the key authors, the person who had drawn up the protocol for the trial, a guy called Neil Ryan. And Neil Ryan was the person who got most nervous about it. What she didn't know when she sent this email to him, Neil Ryan's response was to consult with GSK and say « what do I tell this journalist? ». And they decided to tell the journalist nothing.

So, three days after World Mental Health Day, three days after Paxil had been approved for teenagers who were depressed and the BBC didn't know this, they produced this program here where Shelley Joffre interviews,

this is her here, interviews this man here,

Alister Benbow. And the criticism people have of the program was that this was employing journalists' tricks to make the company person look bad. The lighting was bad on him, people said. Nobody was interested in what he was saying, their were just saying the lighting made him look shifty.

But Alister Benbow was actually trying to explain things that were a little awkward to explain which was he was saying that the most common cause of death amongst teenagers is that they go out to commit suicide, so, you know, we really do need a treatment to help these children. In the trial, in the paper that Glaxo had published, more children became « emotionally labile » on Paxil than on placebo. So trying to respond this way, Alister Benbow was in a very tricky kind of position. This was a politician trying to respond to a journalist that's asking them awkward questions.

As I said, the BBC didn't know that Paxil had been approved by FDA at the point they made the program. They also didn't know that a group of lawyers had gone into FDA a few weeks before the approval and said « *you guys need to be aware that GSK are using this term « emotionally labile » to hide a bunch of very serious behavioural problems not just in the trials of children but in the trials of all age groups.* »

So when FDA sent the letter out, you don't need to be able to read this but what I'm gonna to be doing is I'm going to leave the slides behind so anyone who wants to read the full approval lettre from FDA to GSK will be able to do so. You don't need to be able to read this, you only need to know that at the end of the approval letter, GSK said « *look, we're happy to approve your drug, but we'd like you to explain what « emotionally labile » means and give us a little bit more of a feel for what's hiding beneath these words.* »

So, after the October 13th program, the BBC had 65000 emails in to the program. That, remember, this is 2002. Bruno probably has 65000 emails per day now, but emails were rare back then so when a program has 65000 emails this was extraordinary and a lot of them were from people saying that they had exactly the kind of problems that the problem that the program outlined which is children becoming suicidal, children becoming aggressive, children becoming hooked to the drug unable to get off, having serious problems when they try to get off.

So this led to BBC make a second program which was based on the emails which had been sent to them. It was called « emails from the edge ». What you see here is the MHRA, this is the headquarters of Britain's drug regulator and the reason you've got this image here is, at this point, patient groups were headquartered outside the regulator saying « *look, we're awfully concerned about this group of drugs generally* », and the regulator is under huge pressure.

So the BBC make a second program. In this, they change the way Alister Benbow looks: the lighting is much much softer making him look much more sympathetic. This is the spokesperson for GSK.

But the context of what he has to say is almost even worse. It's « *if we were to give these drugs to all the children in a school, only one classroom of children would become suicidal.* » It's just not a very clever way… I mean he thinks he's saying that it's a very rare problem but the words that come out make the problem look awfully serious.

So, at this point as well, what you don't know is this. Here is an advert. It's a very creative advert, it's got a young teenage boy looking cool, it's even down to the earring in his ear is well-placed. You don't need to be able to read the small text, just read the little bit at the right-hand side. That will give you the message that goes the whole way through this advert.

Things like « *if you're depressed, who should you consult: a TV presenter or a doctor?*

We have total faith in our drugs, so you should too.

Depression is extraordinarily common, and this is the commonest reason people go on to things like suicide.

*Judge Seroxat (*that's is the English trade name for the drug) *by clinical trials, not by trials by media* ». The reason I'm showing you all of this is for an extraordinary fact which is there are a hundred thousand people who work for GSK

and this is an advert the company has produced for its own employees. it's not an advert for the rest of you, this is internal to the company who are very nervous about what the people working for the company will be thinking about what they see on TV.

Okay, so, here is GSK and this is May 22nd 2003. This is a week after the second BBC program where again GSK says there is no problem on our drug. At this point, they're responding to the FDA letter half a year before saying « *we approve your drug but we want you to explain a few things like, you know, what does « emotionally » labile means* ». And this is GSK's response which makes it clear this is a doubling of the suicidal act rate in the clinical trials of children who were depressed and that « emotionally labile » mostly refers to children becoming suicidal.

At the time GSK make this report to FDA, they say there is an increased risk of children becoming suicidal, but it's not statistically significant. So you don't need to worry about it. Russel Katz who's the head of that branch of FDA who approves drugs that we use for nervous problems, writes to somebody else in FDA called Andy Mosholder saying « *look, you're the person who reviewed this drug when we approved it there seemed to be concerns about it* » - the English, as we know are prone to nervous breakdowns or Brexit or things like that but back in 2002, the FDA is saying « *the English are wobbling, they think there might be a problem with this drug, we haven't seen any problem, but we want you to look back through the material you had from the company to see what you spot. »* Andy Mosholder takes three months to do this.

This is the English having their nervous breakdown three weeks after that: English ban all SSRIs for children, teenagers who are depressed. All but Prozac which had been approved a year before. What they say in the media is if you want to give one of these drugs, give Prozac.

A few months later and this is October 2003, it's a year after the Newsweek article. FDA has been through all of the material and this is Tom Laughren, who works for FDA, and he's briefing the media and he's saying « *Look, there has been all this fuss about these drugs causing to have problems, but we, at FDA, don't think it's real problem. We did say a year back in June, just be cautious about these drugs, but we've looked at the material in more detail and we don't now think it's a real problem, but we're going to have a Committee meeting in February 2004 where we'll show the entire world all the material we have and we're calling experts and we'll let them decide what the data looks like and what we should do. »*

So, the meeting's scheduled for February the 2nd 2004, this is where the issues is going to be finally settled. Six days before that meeting, the American College of Neuro-Psychopharmacology has got a working party together of experts.

And you see the ten experts that have been convened here ,and you see three of the experts, whose name has been highlighted in black, are on the working party panel, these have also been authors of study 329. And the conclusion from this working panel which is, generally, in the Unites States, back then, regarded as the Superscientists. These are the people who really know what clinical trials look like, what the data really looks like. So, if these people say there is no problem, then there is no problem. These people conclude that, for the SSRIs for children, they've got access to more than study 329, they say that these drugs work well for children and there are no problems. None of these people wrote the document that said this, it was written by a Public Relations agency called Get Your Message Across.

So, this the agency GYMR and this is their mission statement: « *We know how to take the language of Science and Medicine and translate it into the more understandable language of Health. »* Ok? So their offer to the pharmaceutical industry and regulators is « *if you want to make sure that the entire United States gets the message, we will make sure it is reported in every major newspaper and every media channel right across the country* » and that's what happens before February, the 2nd.

Something else happened which was that Andy Mosholder who's the person within FDA who had been asked to review the GSK clinical trials… The story appeared the day before the meeting in The San Francisco Chronicle, which said that he'd been gagged: he was not going to be let

present his version of the results at the FDA meeting. That got us here, because the most famous whistleblower within the FDA is a guy called David Graham, whom you see here. And Andy Mosholder and David Graham share a common thing, which was they're both christians. Now, when I say Christians, I mean « born again Christians » who so distrust the state that they have their children educated at home. This is an interesting angle on the whole story which I'm gonna leave just there for you guys to think about.

Ok, so, on the day of the meeting, on February the 2nd, FDA had a whole bunch of people, a whole bunch of experts, there were world's media there, there was 72 people who were allowed to make presentations to FDA that could last 3 minutes only. In the middle of the meeting, this document here appears which is an internal GSK document from 1998 and…

I mean, what you see here is only a bit of a six page document that makes it clear that in 1998, just after study 329 has completed, that GSK recognises that their drug did not work in this clinical trial and that was going to be a problem showing it to FDA. Now, what they were going to do was pick out positive bits from the clinical trial, which you see at the end here, and that was going to be published. And that's the Keller paper, it's the positive bits picked out, published with the negative bits hidden.

And the GSK document makes it clear that it would be bad for our adult market if anyone thought this drug didn't work for children, and this is the reason why they were going to take the approach that they were going to take. A few years later, they decided « *we can show the data to FDA and FDA won't spot the problem* ».

And this is the end of the FDA letter to GSK approving the drug I've taken a bit of it and bloated it up so you can read it. And it says FDA are saying « *we agree with you GSK, that you've got three negative trials* - they only did three trials in children who were depressed - *and all three are negative, we agree with you that they are negative, we are still going to approve the drug and we don't require you to mention in the label of the drug that these were negative trials. »*

So, because of the previous document you've just seen, where GSK says « *we've got negative trials and this isn't a good image for our drug, we're going to pick out the good bits out of this trial and publish those* », this lays the basis for a fraud charge that New-York State take against GSK. Further, to be fraud… Bruno may fiddle with the data from some clinical trial that he does or I may think he's fiddled with the data but I don't have evidence that shows that he knew what he was doing and made it clear why he was doing it, then I can't say that there has been a fraud. There has to be « *proof of intention* » for a fraud charge. So the GSK document gave New-York State « *proof of intention* » and they launched a fraud charge against GSK.

And the other thing that happened was congress decided to subpoena Andy Mosholder and ask him what had gone on. I've left one bit out. When FDA had the February 2nd meeting at which the document came to light, the intention was to say that these drugs are fine, they work well and there are no problems and we are going to put the problems to one side. It had become clear, at the meeting, that most of the trials the FDA had of any of these drugs done in the children who were depressed were negative trials. At the end of the day, the meeting, the mood music in the room was « *we can't approve these drugs for children who are depressed other than Prozac which had been approved* ».

So, FDA didn't want to say « *we need to put warnings on these drugs* », they said « *we're gonna wait for half a year, we're going to ask an independent group, we're going to ask Columbia University to look at the what the data looks like* ». The Andy Mosholder report, it's the internal FDA report, it said there was increased risk. But FDA weren't going to let the public see that, they were going to give their own view that there is no increasing risk. So, they had decided that the way to solve the problem was to get an independent group from Columbia University to look at the issues, and they said « *we're going to give them half a year to look at the issues, so we'll meet again on September 14th. »* A week before that meeting, as I said, Congress has began to investigate the issues and has subpoenaed Andy Mosholder and is about to ask the bosses of FDA « *What's really going on here?* » . The other that's happened is GSK have resolved their fraud

action with New-York State and have said we will make the data from our clinical trials publicly available. That hasn't happened by the time that the second FDA hearing happens.

But at the second FDA hearing… this is just a brief vignette and I probably shouldn't include it because it's going to take up time but I'm gonna leave all of the slides behind, they will give you the exact words used by the woman on the left who's the mother of the girl she's holding in her arm who's called Candace. And the Miller family, whom you see here, live straight across the road from Tom Laughren.

She gets up in the middle of the meeting, where we've got the FDA panel at the top of the room which includes Tom Laughren who is the key person in all of this, trying to herd the goats or the sheeps or whatever, you know, the right way to see that there is no problem. She gets up and says, « *look, Doctor Laughren, it's a tricky position I'm in, your daughters and my daughters were in the same school. One of your daughters was in the same class as my daughter. My daughter was given Zoloft at the age of twelve because she was anxious about going to school.* » You know, she had school refusal. It's… I don't know about any of you guys but I had school refusal briefly at the age of twelve and I didn't fortunately get an SSRI, I went back to school and everything was fine, well. Certainly everything was fine since. But Candace was put on Zoloft and a week later committed suicide. And Tom Laughren knew that these drugs, she had become aware that Tom Laughren knew these drugs could do this. So, this was a very dramatic moment in the meeting when she confronts him.

This comes back to this document here and the next bit of the talk which coming back to

this paper here which you have seen. And the twenty authors on it, none of whom write the paper, none of whom have access to the data behind the paper. The paper who wrote the paper is here: Sally Laden.

And she writes a paper which conceals the hazards of the drug. Was that telling lies? The children who had been suicidal have become « emotionally labile » and most people like Bruno back then or me, reading the paper for the first time, wouldn't think that becoming « emotionally labile » was a big deal. The person from GSK who she's emailing with, he's very nervous… he knows what the problems in the study have been, he's clearly nervous about the fact that she's done such a good job in hiding them. He isn't saying to her she's broken the law, but she's done a very good job in hiding what the issues are.

She hasn't broken the law because, well, she hasn't seen the data either. GSK had presented her with numbers and she's making the best job she can of the numbers she's given.

And what becomes clear at this point is, there had been fifteen trials done in children who were depressed, as I say, almost all of these except the Prozac trials are negative. And all of them are either ghost- or company-written. I just want to contrast this with… This is the range of journals whereI have tried to write about this issue about children becoming suicidal, teenagers becoming suicidal on antidepressants and these are all the journals who have refused to review an article even with all the accompanying documents to show them there is no legal risk you're publishing my article. Clearly, the journal that appeals to me the most is: I tried to get this story you're hearing now published in a journal called « Index on Censorship » and they censored what you're hearing now.

So, this goes back to the fraud action New-York State took against GSK. GSK said « *OK, we'll resolve this by giving you… by giving the wider public the data from our clinical trials* ». Now, when the company runs a trial, they prepare a Clinical Study Report afterwards, a CSR. OK? So GSK said they would put the CSRs up on the company website so that every could read the trials done on this drug on children who were anxious, who were depressed, children who were this, children who were that and the diabetes drugs and other drugs as well.

One of the things that was linked into all this and into actually Paxil given to children in particular, was this whole issue about just how fraudulent had the company been. Although the New-York State action was resolved, the Department Of Justice in the United States took an action against GSK. And this action was resolved in 2012 when GSK was subject to what was then the biggest

fine in corporate history. They resolved the case for 3 billion dollars. And this is reported in the BMJ at the end of 2012, which… note, it's a very small notice really within a medical journal and there is very few other notices in any medical journal back this event. Most doctors haven't ever heard of it even though it's of huge importance you'd have thought. It's a small notice that it features the CEO, the boss of GSK then, a man called Andrew Witty.

And here is the BMJ, 3 months later, featuring Andrew Witty, the CEO of GSK in an Obama-type picture. This is the candidate of hope, this the kind of image that was being used by Obama when he ran for presidency. Andrew Witty is being portrayed in the same kind of way: this is the acceptable face of the pharmaceutical industry. And a very clever trick has happened in the intervening period which is that Andrew Witty has signed onto, and possibly been the creator of something that most of you think is a very good thing. It's an initiative called All-Trials which looks like people who are independent of the industry calling on industry to provide all the data from clinical trials. It's not. It's an initiative where industry let people know about clinical trials that they've done and provide a certain amount of data that industry are prepared to let the world see.

So this what All-Trials… No, this All-Trials and my concerns, and this is 2013 when All-Trials is launched and GSK immediately support All-Trials. Is that really what we want? What the world thinks he's been offered is all data. And what we want is all data rather than All-Trials.

So, around this time, there is an initiative and there's an article in the BMJ about this by a man called Peter Doshi who's a man who is the most creative and incisive people around the place. And he's come up with this really good idea about restoring abandoned trials. It's an initiative he calls the RIAT initiative and the idea is when we have the data from clinical trials, if we think it's been misrepresented, we'll… an independent group will access the data and try and produce the right version of what the clinical trial should've looked like. And GSK, of course, have told people that « oh, we've put the company's Study Reports on the web », so Study 329 is exactly the perfect study to say, well, you know, we will rewrite what this trial should have looked like.

One of the interesting things that happened is this, first of all, the original study 329 is an eleven page article. So you see, the number of pages is there. The company Study Report, is something like, on this slide I think you've got around 800 pages, it's something like that. That's for the company Study Report. Their internal version of what the study looks like. The company Study Report however comes with appendices: appendix A, appendix B, appendix C, appendix D, E, F, G and H. When you add a… One of the things that we learned is that when GSK have put the company Study Report up on the web, when you read it closely, it mentioned the appendices but they weren't there. We asked GSK to put the appendices up on the web and they said « *well, ok, we'll put appendices A to G up there but we won't give you appendix H* ».

When you add the appendices A to G and then it brings the number of pages up to five and a half thousand pages. So we got five and a half thousand pages to look up to rewrite what the study really looked like. But of course, I'm sure you like me, would have figured « *what's in appendix H? . Wouldn't that be interesting to have appendix H? »* And appendix H contains what is called the Clinical Report Forms, the CRFs. This is closer to the raw data. It's what the investigator seeing you in the clinical trial fills up, the rating scales, and the report of the adverse effects, things like that.

There's 77000 pages in appendix H. And the problem is, GSK are not prepared to hand it over.

They will… They end up… they agree… and it's hard to know why they agree, I think it's just a mistake in the company. They agreed to let us look at it through a triple-lock portal. We can go into GSK through a triple-lock system here, which means they can see every move we make and everything we look at. And the system chokes off regularly, but we spent a year working on it and end up with a view of what study 329 looks like.

When we begin this, we have been in touch with the BMJ who said they would be very interested to publish a new version of study 329 once we have it done. And if you've ever tried to publish with the BMJ, you have gone on the website and you see that they tell you that, actually, it takes roughly 8 weeks from the time your article goes into them to the time you have an answer back from them as to whether they are going to publish or not. That's usually two people who review

your article, it might be three. We have seven people review our article. It's reviewed seven times. It's accepted several times and then unaccepted several times. It goes to GSK for review. A year later, it's not published. We spend a year working on it, we spend a year working on BMJ in order to try get it published… and we're not getting anywhere.

In the end, it's getting published, it's been published close to four years ago now and this is what the BMJ front cover looks like. It looks cute and it looks like BMJ are very proud of the study

but if you want to know the full story of what went on, you can go to study329.org here where we've got all of the internal documents and the history of the whole saga.

Just to give you a brief view of what the results look like. GSK claimed the drugs works well in children who were depressed, we analysed the efficacy data in all sorts of ways, meaning three different ways. We were told by the reviewers when we say « *look, the results are negative* », « *well, try this way!* ». Well, we do and there's no way you can torture the data to get a positive result out of it. Well, the other things I should mention to you is, this is a 8-week trial as you see here, the protocol was for 32-week trial. That's a 6-months follow-up after the acute phase of the trial. GSK never published the 6-month follow-up, that remained unpublished.

The really interesting thing about this trial, though, is not about does this drug work or not, it's a trial about how to hide the problems and out of it has come my views that « *RCT are the Gold Standard way to hide adverse events* ». And this is a few of the things that you can do. When events happen in the trials, you have to have a coding system and GSK use an obscure coding system which allowed them to code suicidal events as « emotional lability ». This is not illegal but, you know, all trials use a coding system of sort. There was a failure to transcribe adverse effects from the Clinical Report Forms into the company Study Reports. There's grouping of adverse effects, and I'm going to show you a few of these. Let's leave this table here because it's a bit too busy…

This is the coding system. This is one the most commonly used coding system and the cartoon here gives you what I think is a good representation of what happens which is you've got human diversity that goes in one side of the coming… coding system and everybody comes out looking much the same colour on the opposite side of the coding system.

But aside from that, there are tricks like this: there are problems like headache that could be neurological or could be psychiatric or could be cardiovascular or could be coded under general. And there's a lot of headaches happening in clinical trials, just as there is a lot of dizziness and if you move these round different bigger coding groups, and particularly, if you include the psychiatric effects in the neurological group, then on headaches also, you can make any problems, any behavioural problems disappear.

So if you look at the bottom there, that's the original Keller paper, which you'll see five children became « emotionally labile »… actually they report six but, of the six, five have become suicidal and in the trial Paroxetine is compared to Imipramine, and you see the number of people who have become suicidal on it. And there's one person who has become suicidal on placebo. When GSK report to FDA, when FDA say « *what's « emotional lability » all about?* », GSK writing half a year later to FDA and say « *actually, there's more children who became « emotionally labile » and this term means they became suicidal* ». Then you see, what they reported to FDA here, I've got it under SKB because it was Smithkline-Beecham who were doing the reporting rather than GSK. But, you see this, a lot more suicidal events in this trial that FDA are being told for the first time that there is a lot more events than they report. When we get access to the raw data which is up on the top, you see that there are more events again. We have three times more events than were reported in the original article. And we don't have all the events, it would be a much longer lecture to tell you about all the events which have come to light since.

This is the continuation phase. What you saw on the previous slide is the efficacy in the first 8 weeks. What you see here is what happens to children when they take the drug for the next six months. And again, you can't see any benefit for the drug over placebo.

This is the suicidal events that happened during this next 6 months and again you see there is much more on active treatment than there is on placebo.

And the worse phase of all is the withdrawal phase and GSK didn't report on this at all. The highest rate of suicidal events happens when you stop the drug whether you stop in the acute phase, whether you drop out at that point or whether you've been on the drug for half a year and then stop. This is at a point where GSK were denying that there was any dependence and withdrawal from this drug at all.

I'm gonna skip that because it's a different story.

Ah, a lengthiest one, I'm just going to take you back to this slide. We took a year to get this article published in BMJ and one of the problems was we noted headaches and this was… this is moving all over the place to suit GSK, it seemed. And one of the editor in BMJ who handled our article just happened to be a person who is a neurologist who'd written a book on headaches. And she was very concerned at us, raising questions about what's the best way to code headaches. And she was the key person who held our article up for a year. This got interesting when I found this book and googled her, the story became even more interesting.

When GSK were sued by the Department Of Justice in the UK… in the US, and ended up paying 3 billion dollars, one of the law firms representing them was Ropes and Gray. When GSK recently ran into trouble in China, the only law firm defending them was Ropes and Gray. And Elisabeth Lauder's husband is a senior partner in Ropes and Gray.

So is this one, just one very obscure… so, this is my final point, I promise you, I'm going on much too long… But, we run controlled trials because open trials, we figure, are unsafe. You have a new drug and you give it to doctors who are enthusiastic about new drugs who give it to patients and you universally report tremendous benefits. So, when the SSRIs come out, doctors in the United States, with a little help from the pharmaceutical companies, write up articles about, you know, they've given SSRIs to teenagers and in every case these drugs have done wonderfully well. So, you know and I know this is why we do controlled trials: open studies like this are biased. So, we've got to control the bias with the controlled trial.

So, as of 2004, I don't know, this is again all too small, you're gonna have to trust me probably on this… As of 2004, and all this fuss blows up, these are the controlled trials that have been done. The ones that have been published have all been reported as positive. The ones who have been published have been ghostwritten or have been written by the company. FDA and MHRA and EMA say they now all agree that most these trials were negative except for the Prozac trials which were positive. If you look at this chart I have N against the Prozac trials as well. The trials that FDA… when they approved Prozac, the trials of Prozac were negative trials. They were not positive trials. There is not a single positive trial as of that point in time in teenager who were depressed.

There's… and this is a little out of date, there's not a single positive trial since in children depressed. And trials have continued since 2004. There are more negative trials in Prozac in children, I mean, all, there's… all the trials in Prozac in children who were depressed are negative and there's more of them for Prozac than any other drug. There is now over 10000 children who have been recruited to randomised trials for these drugs and there's no positive evidence.

Just to go back here, you see, the left column is N, the next column is XS. There is an excess of suicidal acts on active treatment and the most interesting trial here, in this column is one run by the NIH, supposedly which was independent from industry where, under Prozac, if you look at the Prozac trials you see excess in brackets 34 v 3. In this trial, there are 34 suicidal acts on Prozac versus 3 on placebo. There's seven major publications about this trial but it's very difficult, you will not spot the 34 versus 3 suicidal acts on Fluoxetine in any of these publications.

So you'd have thought if we have 30 negative trials that we'd have stopped using this drug. This is the whole point behind controlled trials, when the controlled trials come in negative, it means we stop using the treatment. This is the greatest concentration of negative trials for any indication

in any age group ever done but antidepressant are now the most commonly used drugs by teenage girls barring oral contraceptives.

Thanks.

(Applause)

BH: Y-a-t'il des questions? Merci David. Thank you, David for this brillant talk. Y-a-t'il des réactions, des questions?

Pr Behrouz Kassaï: Thank you very much for the nice talk. I have just one question, one comment about the difficulty we have to assess the adverse events. For instance, you cite the example of the family who has lost a child, a daughter. We're not sure that this is the drug that is the cause of the suicide on one case. That is the difficulty. If you say that we need controlled trials, we cannot also say, at the same time, that when we're seeing an adverse event, that it is because of the drug. So I want you to comment on that.

DH: OK, well. To see clear (?). The rate to which children in controlled trials of these drugs go on to become suicidal, because there is a doubling of the rate of children becoming suicidal on these drugs on controlled trials, they now carry a blackbox warning. At least, that's the story that many of you hear in the room believe. In fact, the rate to which adults go on to become suicidal on these drugs is exactly the same as children. The reason we got a blackbox warning in the case of children is it's been difficult to show a benefit against which the risk can be put. In adults, we don't warn about the risk in the same way, because of a supposed benefit, we don't want to tell people « you may become suicidal on this drug » in case they get scared of seeking treatment. But I want to come back to adults. This story did not begin in 2002 on World Mental Health Day. Twelve years beforehand, there had been an article about adults becoming suicidal on Prozac. And the interesting about the article was that the doctors were very experienced people, very senior people linked into Harvard. Some of the most respectable and senior people in the field who said, you know, « this is interesting, we've got patients who have to us who said « Doctor, I've been depressed and suicidal for years, but this was very different. What the drug is causing is very very different from the illness causes ». I think that's great evidence that the drug causes the problem, particularly when you stop the drug and the problem clears up. If the persons haven't actually killed themselves, you stop the drug and the problem clears up. And as they did, as this group did, others linked to them did, they gave the drug in one extraordinary famous case, this particular woman was given the drug she became… Well, one of the things the drug does is they can cause a condition we use a strange word for called akathisia, this means « agitated ». you end up in a state of turmoil. She ends up in a state of turmoil and she jumps off the roof of the building in which she's been treated. And fractures her hips and legs and ends up in a wheelchair.

But, she's feeling emotionally a lot better, the… because she's been in the hospital (…) for hips and legs the, she's off Prozac, the agitation goes away. And at her instigation, they give her Prozac again and she becomes agitated again. She has the same feeling… They feel safe and she feels safe to take the drug again because she's now in a wheelchair and they're keeping an eye on her. She's not going to jump off the building. There are a lot of reports of people becoming suicidal in this way on this group of drug, the problem clears up and reoccurs when you expose the person again when you expose the person again to either the same drug or a different drug from the same group. So you can fool the person saying that you're taking from a completely different group but give them a SSRI again and they become suicidal again. This is better causal proof than from controlled trials. And I have a shake of the head here saying « no », but we can disagree on this point but this, I think, is much better proof. But we can open up and ask the rest of you what you think.

(…)

What do you think of the fact that it's not doctors who opened this issue up? It's a person who has nothing to do with healthcare, it's a journalist who opened the picture up. What do you think of the fact that it's not a man who opened the picture up, it's a woman. And that most of the adverse events of drugs that, sort of, have been brought out in recent years have been put on the table by women, not men? Anyone, any thoughts?