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Taken on trust

Panorama: Taken on Trust

Generic drugs

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Introduction

We take it on trust that the drugs our doctors prescribe are safe and effective. But this special investigation exposes huge failings in the system of medicines regulation that is supposed to monitor drug safety. It reveals how patients' lives have been put at risk as a result.

Panorama takes a unique journey inside the secret world of the medicines regulator and discovers that it's been sitting on crucial safety information about one of Britain's most widely-prescribed antidepressants for over a decade.

For the last two years, Panorama has been investigating claims that Seroxat can cause addiction, self-harm, aggression and even suicide. The medicines regulator always denied there was evidence to back up these claims. But now the programme reveals that, not only is the evidence there, it's been lying dormant in the regulator's archive for at least 13 years.

One insider tells the programme: "I have little confidence that the drugs they're licensing day by day are being licensed in a way that I would feel appropriate and - I have very little confidence in drugs that have been regulated in the past."

What the programme uncovers has led to some of the most influential names in medicine asking if we're being told the truth about the pills that we take. Dr Mike Shooter, President of the Royal College of Psychiatrists, says: "It has serious implications for the whole of psychiatry, it has serious implications for the whole of medicine."

"I think a few years down the line we are going to be talking about this with many more sorts of medication." Forty years after the thalidomide tragedy prompted the setting up of drug safety monitoring, the regulator is accused of letting down the patients it's supposed to be there to protect. If you have been affected by any of the issues raised by tonight's programme and want to be put in contact with an organisation that can provide information and support, you can call the BBC Action Line. It is recommended that you do not stop taking any medication before consulting with a doctor.

The Action Line no is: 08000 688 456

Link: <http://news.bbc.co.uk/nol/shared/spl/hi/programmes/panorama/transcripts/takenontrust.txt>

PANORAMA

TAKEN ON TRUST

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SHELLEY JOFRE: Every one of us uses prescription drugs at some time in our life. We take it on trust that these pills are safe. But are they?

JUDY BARTLETT: The suicidal thoughts only happened while I was taking the drug, they've never happened before or after.

JOFRE: Some of the most influential names in medicine are now asking if we're being told the truth about the pills that we take.

MIKE SHOOTER: It has serious implications for the whole of psychiatry, it has serious implications for the whole of medicine.

JOFRE: For more than two years, Panorama has been investigating your concerns about Seroxat, one of the world's most controversial drugs.

SARAH THOMPSON: I'd never thought about suicide before I took Seroxat and when I was taking it. I was obsessed about death, it was part of my everyday life.

JOFRE: What you've been telling us has exposed major failings in this country's system of medicines regulation.

CHARLES MEDAWAR: They failed. They failed miserably and they caused a huge amount of distress because they did.

JOFRE: This man has been inside the secret world of the medicines regulator. He found that for years it missed crucial safety evidence on Seroxat; a failure which must raise concerns about other medicines we take.

RICHARD BROOK: I have little confidence that the drugs they're licensing day by day are being licensed in a way I would feel appropriate and what's even more concerning I have very little confidence in drugs that have been regulated in the past.

DAVID HEALY: I think in due course we may look at all of this and think this was one of the biggest

medical scandals ever.

JOFRE: Now the regulator's handling of one drug calls into question whether prescription medicines should be taken on trust. This dreary office block in south London is home to a very important government agency. The Medicines Healthcare Products Regulatory Agency or MHRA. You've probably never heard of them. They're a kind of pill police.

Sir ALASDAIR BRECKENRIDGE

Chairman, Medicines Healthcare and products Regulatory Agency

The primary role of the MHRA is to protect the public health. It also has got a responsibility to ensure that only drugs which are effective and safe come to the market and remain on the market.

JOFRE: The MHRA maintains its one of the finest regulators in the world. But that boast has been seriously undermined by your complaints about Seroxat. It's one of the most widely prescribed anti-depressants in the UK and was licensed by the regulator 13 years ago. Over the course of two years, Panorama has investigated your complaints and uncovered evidence that Seroxat can cause aggression...

MARTIN HAZEL: I started thinking that everybody was out to get me. I started to feel angry and murderous. I wanted to kill my partner and my family. I've never felt like that before. I sat on the edge of the bed holding my knees up against me because I knew that if I moved I would kill everybody.

JOFRE: Evidence it can cause suicide...

JAKE EMMS: My father was on Seroxat for four days. On the fourth day of taking them he was in possession of a hunting gun and he went to a local wood and shot himself.

JOFRE: Evidence it can harm children...

LAURA BANNING: When I was on the tablets I did self-harm. I would use any sharp thing like scissors, knife, and I would just put the point to my arms and just scrape until it bled.

JOFRE: And evidence it can leave you hooked.

SARAH VENN: I came home for Christmas one year and forgot to take my drugs with me and within a day of not having Seroxat I was going absolutely berserk. I was threatening to drive 100 miles back home to get a pill - to take it. I was driving around pharmacists begging them to give me a packet of Seroxat.

JOFRE: Seroxat is one of a group of antidepressants known as SSRIs which got the Regulator's seal of approval in the early '90s. They're marketed to treat all sorts of anxiety, stress and depression and have

helped millions of people. But they're also hugely controversial. Five times the regulator has reviewed the safety of these drugs. Five times they've been given a clean bill of health. But in the case of Seroxat - each time the regulator got it wrong; failing to spot crucial safety information, some of which has been under its nose for 13 years. It's a story that raises serious questions about the system of medicines regulation in this country.

DONNA WOODMORE: The worst I personally feel is when I attacked my daughter. I held her head in my hands and I was hitting her head on the floor over and over again.

THOMAS STEVENSON: I told him explicitly about the dreams I was having and he just started to laugh so I said to him, 'doctor, I don't find this very funny because I'm dreaming about murdering children.

JOFRE: This wider picture has only now become clear because this man – the head of Britain's largest mental health charity - took a unique nine month journey into the heart of the regulatory system.

RICHARD BROOK

Chief Executive, Mind

I was putting the consumer voice right to the heart of drug regulation really in the Seroxat issue. I think I was quite open-minded in the early days about what would happen, you know, I was very hopeful that my inclusion might actually make a real difference, make real change.

JOFRE: Richard Brook was invited to sit on a sit on a sixth safety review of the SSRIs. It's become known as the Expert Working Group. The government ordered it to be set up in April last year in response to mounting controversy about the drugs. Richard Brook was the first patient's representative ever to sit on one of these reviews, it gave him access to a world that's protected from scrutiny by draconian secrecy laws, a world he says where patients' interests come last.

BROOK: I think I've been totally let down really by the regulator. Actually, the most important thing here, I mean at the of the day it's we.. we're taking the medicine, it should be the most important thing and it's the least important thing, they're bottom of the list.

JOFRE: One of the first things Richard Brook discovered was how the MHRA had failed to protect some of the most vulnerable patients of all, children. Sarah Thompson was one of nearly two dozen children who contacted us after our programme in October 2002. She was just 16 when she was prescribed Seroxat for depression. Until then she'd never been suicidal or self-harmed.

SARAH: I would cut myself mainly, and then I started to burn myself and found other methods, but it was mainly cutting myself to start with.

JOFRE: And this was within the first week of taking Seroxat?

SARAH THOMPSON

Yes, it was the very first week I took Seroxat.

JOFRE: Had you ever done anything like that before?

SARAH: No, I'd never even thought about it. It's not something that had crossed my mind until I started taking it.

JOFRE: At the very first meeting of the Expert Working Group last summer, Richard Brook was shown confidential clinical trial data from the manufacturers of Seroxat, GlaxoSmithKline, the results of extensive testing of the drug in under 18s from years earlier. It appears this was the first time the regulator had ever investigated whether Seroxat was safe for children in spite of the evidence previously uncovered by Panorama.

Was there any evidence that the regulator had been concerned about the effects of Seroxat in children?

RICHARD BROOK

Expert Working Group May 2003-March 2004

No, not as far as I'm aware. I mean I've had all these reviews through the 90s and as far as I know, they'd always given the drug a clean bill of health for adults, and although it's not licensed for children, I mean they knew it was being used, from the data they had it was being used in children, it was never causing an issue for them.

JOFRE: Most medicines are only licensed to treat adults but there's nothing to stop doctors prescribing them to children. The MHRA knew many thousands of children were being prescribed Seroxat and that concerns were being voiced about the drug, yet it didn't ask GlaxoSmithKline to provide evidence that Seroxat was safe for under 18s. This failure turned out to be disastrous for teenagers like Sarah Thompson.

SARAH: I did attempt suicide. I attempted to slit my wrist and take an overdose so it did get very bad. I'd never thought about suicide before I took Seroxat and when I was taking it I was obsessed about death. It was part of my everyday life.

JOFRE: In April last year we put these claims to GlaxoSmithKline. Their defence of Seroxat was robust. And you still think that the drug could be safe for children?

Dr ALASTAIR BENBOW

Head of European Psychiatry, GlaxoSmithKline

Panorama interview April 2003

Absolutely. It could be. We haven't got a license in children yet. I feel sorry for anybody who has any side effects from treatment or indeed has experienced the terrible symptoms of depression. We are trying to help people. The evidence, however, is clear, these medicines are not linked with suicide, these medicines are not linked with an increased rate of self harm.

JOFRE: But we now know that's not true and it's surprising that Doctor Benbow said it was. Just a month later GlaxoSmithKline sent a confidential dossier to the MHRA and it was Doctor Benbow himself who went to meet them to discuss it's contents. The company was confident it would lead to a licence extension allowing Seroxat to be marketed for the treatment of certain anxiety disorders in under 18s. But the dossier contained a bombshell. **GlaxoSmithKline's own clinical trial data revealed that the drug simply didn't work in depressed children. Worse still it made them up to three times more likely to self harm and attempt suicide than depressed children who were just given sugar pills. This was evidence the regulator had never seen before.**

RICHARD BROOK

Expert Working Group May 2003-March 2004

It was really a shock to them. In discussions directly with me officials were saying we have defended this drug for a decade. There has never been a sign as far as we're concerned about an issue here, and suddenly we're faced with this. And as that story unfolded it becomes clearer and clearer that the sort of way the information is put into the MHRA's possession, all of that is somewhat suspect to say the least.

Prof Sir ALASDAIR BRECKENRIDGE

Chair, Medicines Healthcare and products Regulatory Agency

It was a very dramatic change in our thinking about Seroxat in children. Remember Seroxat has never been licensed in children. It has never been licensed in children at all, but nevertheless practitioners have, on their own behest, have used it extensively. Our best evidence is that some 7,000 children a year were.. or children and adolescence were receiving Seroxat.

JOFRE: Faced with GlaxoSmithKline's evidence the MHRA acted quickly. Within a fortnight Seroxat was banned for use in depressed children. Ever the optimist Doctor Benbow tried to minimise the damage when we spoke to him in June last year.

Dr ALASTAIR BENBOW

Head of European Psychiatry, GlaxoSmithKline
Panorama interview June 2003

This increase is small. It's 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, so it's a small but important signal...

JOFRE: A small class of suicidal children! That's not what Doctor Benbow told us in earlier interviews or what doctors were led to believe by the few Seroxat children studies published in medical journals. This episode has exposed a dangerous loophole at the heart of the regulatory system. Believe it or not, there's no legal requirement for drug companies to publish their trial results. So if they're not favourable they often aren't published.

If you Accident and Emergency concerned about any of the issues raised in this programme, an actionline number will follow. You should not stop or change any medical treatment without first consulting your doctor.

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Calls are free and confidential

JOFRE: For Doctor Tim Kendall this almost proved disastrous. He's part of a team that advises the NHS on the best treatments for doctors to use. Last year, using just published trial data, they were about to recommend that Seroxat and the other SSRIs could be prescribed to children for depression, but then the team asked the regulator for the unpublished trial results. These turned the recommendation on its head.

If you'd relied solely on the published data, what would your recommendation have been?

KENDALL: It would have been that we probably would have said use these drugs, and then there would have been children who might well have killed themselves further down the line as a result of our recommendation.

JOFRE: So what did you think as a scientist when you realised that there was a huge gulf between what was published and unpublished?

Dr TIM KENDALL

Co-Director, Mental Health Guidelines for
National Institute of Clinical Excellence

We were flabbergasted. We were completely taken aback. None of us had expected that the outcome of this would be that we would have completely changed our recommendations for the use of these drugs.

JOFRE: Six months after banning Seroxat for children the MHRA banned all the other SSRI antidepressants except Prozac for use in depressed children. The President of the Royal College Of Psychiatrists is appalled that negative trial results could have been kept from child psychiatrists like him.

Dr MIKE SHOOTER

President, Royal College of Psychiatrists

I personally felt cheated and heaven only knows what the children, adolescents and their parents and their GPs on the other end of that felt, very much the same. I also felt very confused because I know that with some of my patients in the past the SSRIs have been important in their recovery as well as all

the other things that I might be doing with them and yet, suddenly, the balance between risk and benefit was quite clearly tilted in a different way.

KENDALL: If we can't be sure if there are trials that are being withheld or not published for.. you know.. sometimes years on end, this absolutely shakes the whole foundation of scientific medicine.

JOFRE: We wanted to ask GlaxoSmithKline just how long they'd been aware of the danger Seroxat poses to depressed children. But, on this occasion, they decided not to do an interview. In a statement they told us they only saw an indication of a problem in May last year when they reviewed the results of all the children studies they'd ever done. But the decision to ban the drug was based on three depression trials, and the last one of those finished in July 2001. The company doesn't explain why it took nearly two years to pass on the results of these to the MHRA.

Did GlaxoSmithKline act promptly in getting this information to you?

Prof Sir ALASDAIR BRECKENRIDGE
Chair, Medicines Health and
products Regulatory Agency

This is a matter which we are investigating at the present time. There is an investigation going on, being conducted by the.. one of this.. the inspection and enforcement sector of the agency and with lawyers to decide whether or not they did.

JOFRE: Do you think two years is an acceptable delay?

BRECKENRIDGE: That is what is being investigated by the lawyers at the present time.

JOFRE: But during that time we both know that children were being prescribed a drug which we now know is harmful. What do you say to them and to their parents about why that was allowed to happen?

BRECKENRIDGE: When we received the information we acted with great rapidity.

JOFRE: I understand that but...

BRECKENRIDGE: We acted within two weeks of receiving the information.

JOFRE: I understand that but why were you not in a position to get that information from them earlier? Did you not know that they were doing studies in children?

BRECKENRIDGE: That is what is under investigation at the present time.

JOFRE: Might criminal charges be brought then?

BRECKENRIDGE: That is a possibility.

JOFRE: Richard Brook believes the only reason GlaxoSmithKline gave the MHRA the results at all was because they wanted a children's license.

RICHARD BROOK

Expert Working Group May 2003-March 2004

I'm absolutely certain that if Glaxo had not been going for an extension license the expert group would not have got the paediatric information.

JOFRE: And so children could still have been being prescribed a drug that's harmful to them.

BROOK: I think that's certainly a hypothesis that you can actually believe has got a lot of truth and credibility to it.

JOFRE: When the MHRA announced the Seroxat children's ban last summer it gave no hint that GlaxoSmithKline could have been aware of the safety concerns for years. It said the ban was based on new information. Richard Brook says this was misleading.

BROOK: I felt that the MHRA seemed to suggest it was new information to them and to Glaxo and that I didn't think was fair, and I had several discussions after the press conference on the very day with the head of post licensing expressing my concern. We had a meeting subsequently and in the end we were told that it would be looked at criminally and the only thing that we did to raise the issues would be in breach of the procedures and the law that surrounded these sorts of things. In other words we were warned off about making a fuss about it.

JOFRE: We got hold of a confidential internal GlaxoSmithKline memo. It shows that the company knew that Seroxat, also known as Paroxetine, didn't work in depressed children as long ago as 1998.

SSB CONFIDENTIAL – FOR INTERNAL USE ONLY – October 1998

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

JOFRE: In other words, publishing negative trial results in children could seriously damage Seroxat's health and GlaxoSmithKline's profits.

What did you think personally when you read that memo?

Dr TIM KENDALL

Director

National Collaborating Centre for Mental Health

I was disgusted, horrified, that people could seriously consider withholding information about the

prescribing of a drug that may do harm to children and certainly suggest that they don't work. To withhold that, or to suggest that should withhold that, I think.. I think is horrific.

JOFRE: The company says it didn't withhold the information, that some of the trial results were presented at American scientific meetings five years ago, but none of the results were published here in Britain, and the MHRA only received the full trial data last year. The evidence of the danger Seroxat posed to children was mounting in clinical trials for years, but the regulator remained blissfully ignorant. Meanwhile British doctors were allowed to prescribe a harmful drug to thousands of children.

SARAH THOMPSON

Looking back at what happened to me because of Seroxat and the great effect it has had on my life and to my relationship with my family and my future, I don't think that the regulators are doing their job properly because they allowed me to take a drug that has in effect taken away a part of my childhood.

JOFRE: The whole children's controversy forced a complete rethink about the safety of Seroxat. Straight afterwards the expert review group was set a mammoth task. To re-examine the original clinical trials done in all age groups. One of the first questions the group was asked to consider was could Seroxat make young adults suicidal too. Adrian Keegan was 19 when he took Seroxat.

CHRIS & DAWN KEEGAN

I used to do some shopping for Adrian. He used to come to collect I here, but on this Friday night we decided to take it to his flat and we got no answer when we knocked on the door, so we thought he'd gone out. But then on the Saturday morning we noticed the lights were still on.

I dropped you off and then I went back to the flat, didn't I Dawn, to his flat, to check on him. I knocked on his door, got no answer. And then I looked through his letterbox and I noticed his keys.. his door keys were on the storage heater in the hallway. I knew that he was in so I knocked again, couldn't get no response so I tried to force the door and I couldn't, couldn't open the door. So I came back home and I got a chisel bolster. Ohhhhh... and then I broke into his flat and... and then um... I found him then in the bathroom. He'd hung himself.

JOFRE: Adrian's parents contacted Panorama after our first programme. Dawn Keegan had originally taken her son to the GP for help in controlling his temper. She hoped perhaps to get him on an anger management programme but Adrian was prescribed Seroxat instead. His parents noticed a difference straightaway.

DAWN: He sort of changed, he was like very quiet within himself. Even his friends commented it wasn't Adrian, he was like.. well then he wasn't saying much at all, or jokey, he wasn't jokey like he used to be.

JOFRE: The sixth and most recent review of SSRI antidepressants has discovered that Seroxat may indeed make young men like Adrian Keegan suicidal. The Expert Working Group asked GlaxoSmithKline to reanalyse its original clinical trial results. When they did they found evidence to suggest that 18 to 29

year olds may be at an increased risk of suicidal behaviour. So why did it take 13 years to uncover this crucial information. Again, Sir Alasdair says they're looking into it.

Prof Sir ALASDAIR BRECKENRIDGE

Chair, Medicines Healthcare and
products Regulatory Agency

That is a matter which is under investigation just now, whether or not there was evidence at that time in different age groups which we did not have access to.

JOFRE: Well there was information, did you just not analyze it at the time, or was it not presented to you?

ALASDAIR: This is a matter which is under investigation at the present time. Whether or not the evidence was presented, whether it was analysed and what happened to it, this is part of the ongoing investigation.

JOFRE: GlaxoSmithKline keeps its own database of side effects that doctors and patients report to them and it says these are passed on to the regulator. We've discovered these reports, some of which go back many years, support what's in the original trial data. They suggest that young adults and males may be at an increased risk of self harm, hostility and suicidal behaviour within the first month of taking Seroxat.

Adrian Keegan was on the drug for just 26 days. But the patient information leaflet that accompanies the drug carries no warning addressed to young adults. Would it have made a difference do you think?

CHRIS KEEGAN: Yes, because you'd be able to keep an eye on the person that's taken the medication for a start off. You'd be able to monitor and be able to look after them properly, I think so.

DAWN KEEGAN: I wouldn't have let him go on it if that information had been put on it. I wouldn't have took the risk. It's just.. it's not worth it.

JOFRE: The leaflet which is approved by the regulator didn't warn Adrian and his family. Even now doctors haven't been properly warned. The only clue is on the MHRA website and all that says is that doctors should carefully monitor young adults after prescribing Seroxat.

It's appeared on your website since April but why isn't it in the patient information leaflet?

BRECKENRIDGE: The patient information leaflet will be altered when the current review is complete which will be towards the end of this year.

JOFRE: But that's quite a delay. I mean you've known this information for a while, why are you waiting to tell people.

BRECKENRIDGE: In fact in the.. as you say, on the website this information is available, it is available ah...

JOFRE: Yes, but patients don't tend to read the MHRA website. Why is it not in the patient information leaflet?

BRECKENRIDGE: Well there are several aspects of the patient information leaflet which are currently being revamped at the present time and this will be one of them.

RICHARD BROOK

Expert Working Group May 2003-March 2004

The regulator may well have created a situation where people have died. It makes me very sad for the families and the people that I've got to know during this time dealing with Seroxat. Very sad that they've encountered such tragedy and we'll never know whether that tragedy could have been prevented by better regulation. We'll never know but we'll always have the question.

CHRIS & DAWN KEEGAN

We worry about the other children not on a weekly basis or a day to day basis – on a minute and second basis. Totally affected us. Changed our personalities, changed our lives, everything, hasn't it Dawn.

JOFRE: Remember, the information about young adults was in the original trial data given to the regulator in the late 80s. So how could it have missed such an important signal? The answer may lie in the licensing process. The MHRA takes an awful lot on trust when it makes its decisions about a medicine's safety.

Each clinical trial produces a huge amount of information and this raw data is summarised by the drug companies. The regulator then relies on these summaries. It rarely studies the raw data itself. With the SSRIs though, there have been five safety reviews since 1991. Each one of these was an opportunity to spot what was missed originally. Richard Brook says that none of these reviews examined all the raw data either.

How rigorous do you think the previous reviews of the SSRI antidepressants were?

BROOK: Well sitting here in 2004 they're not really worth the paper they're written on. The reasons for that are complex but basically it seems that they were not robust, they were not rigorous and they didn't look at original data, and so they seemed to be as much use as paper in a waste bin.

JOFRE: Panorama can reveal that this current review is the first time the raw data from the original clinical trials has been properly analysed. The Expert Working Group is now considering whether there is evidence lurking among this data that Seroxat may make adults suicidal. The group is expected to

publish its findings later this year. But one of the most respected figures in British psychiatry is already convinced a link exists.

I think the evidence that these tablets can cause suicidal feelings is now absolutely clear. I don't think really we can dispute it.

Prof PETER TYRER
Head of Psychological Medicine
Imperial College

In our own work we found that it's related to the sort of person you are. Your personality determines whether you have the problems whereas some people without certain types of personality characteristic don't have them. So we need to identify the people who are at risk and then we can say well look, I'm not going to prescribe this for you, even if you wanted it, because I think it could induce suicidal behaviour.

JOFRE: One psychiatrist above all others has insured that we've heard information about Seroxat that its manufacturer would rather we hadn't. On Panorama's previous programme Doctor David Healy explained what he'd found in the secret archives of GlaxoSmithKline during an American legal action, evidence he says proves the company has known all along that Seroxat can make all age groups suicidal.

Dr DAVID HEALY
Director
North Wales Department of Psychological Medicine

The data that went in from the clinical trials on these drugs done 15 to 20 years ago makes it absolutely clear when you add the whole thing up that actually the rates at which people become suicidal on these drugs, and this isn't just children or young adults, this is any age group at all, is 2 ½ times greater on the drug than it is in people taking placebo.

JOFRE: Doctor Healy only saw this data after he was granted a court order as an expert witness in the legal action. He told the British regulator what he found five years ago.

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HEALY: Back when I approached the regulator first at the end of 99 I thought this is an issue that could have been sorted out with him some months. I guess pretty well every year for the last five years I've thought it'll get sorted this year. But it's still not sorted.

JOFRE: Not only is it still not sorted but Doctor Healy's professional reputation has taken a battering.

HEALY: I've heard myself being branded as a 'hired gun' and a bunch of other things as well. I had people call me from literally the four corners of the world and say "Hey, we've had people come through here recently who've said that really we oughtn't to have any links to Healy at all because he's trouble and he's going to be in trouble".

JOFRE: Isolated from mainstream medical opinion, Doctor Healy has also been ridiculed by GlaxoSmithKline.

So you're absolutely confident that Doctor Healy is wrong on this issue and will be shown to be wrong.

Dr ALASTAIR BENBOW

Head of European Psychiatry, GlaxoSmithKline

Panorama interview April 2003

Yes, absolutely. Not only that but Doctor Healy has made the same claims about a range of other medicines. He made the same claims about Prozac, he made the same claims about a range of other SSRIs. On every occasion he has been found to be wrong.

JOFRE: Now though, Doctor Healy is attracting support from the very highest level in British psychiatry.

Dr MIKE SHOOTER

President, Royal College of Psychiatrists

I think that anybody like David Healy, who has spent many years now, trying very hard at great personal cost, to put over what patients are saying, to put over the cause of freedom of information, to point out that we might not have all the information, that there might be less therapeutic benefit and greater risk than we currently understand deserves my admiration.

JOFRE: Do you think he's been vindicated?

SHOOTER: I think David's day is here.

JOFRE: But the Chairman of the MHRA is still completely at odds with Doctor Healy. He says a recent analysis of 300 clinical trials – all funded by GlaxoSmithKline – proves the drug is safe in adults over 30.

Prof Sir ALASDAIR BRECKENRIDGE

Chair, Medicines Healthcare and
products Regulatory Agency

There is very good clinical trial evidence that these drugs do not cause suicide, they do not cause suicidal thoughts in adults. There is a very large database.

JOFRE: They might cause them in young adults, they do cause them in children, but they absolutely definitely don't cause them in people over 30?

BRECKENRIDGE: In the adult population the drugs are effective. There are many, many studies to show that. There are.. in over 300 studies which have been analysed and studies using epidemiological databases the drugs do not cause suicide, they do not cause suicidal thought.

JOFRE: The database Sir Alasdair refers to actually reveals that the risk of suicidal behaviour increases in the first month after starting Seroxat. But he claims that is because of the illness, not the drug.

Source: Journal of the American Medical Association, July 2004

BRECKENRIDGE: There is a period of time when the drug does not act, it takes a period of 3 or 4 weeks before effect.

JOFRE: But it's in your bloodstream immediately. Are you suggesting it has no effect on you?

BRECKENRIDGE: It has no beneficial effect for some 3 or 4 weeks.

JOFRE: But it might have a detrimental effect.

BRECKENRIDGE: And during that period of time there is a risk of suicide which remains from the period as before, and that is the period when the practitioner must monitor the patient very carefully.

JOFRE: From Professor Tyrer's careful monitoring of his patients he's seen even that Seroxat can cause suicidal feelings, feelings quite distinct, he says, from the patient's illness.

In your view does Seroxat make some adults self harm and become suicidal?

Prof PETER TYRER

Head of Psychological Medicine

Imperial College

Yes, I've had a patient that I treated myself who found this effect. He found it only on a certain dose and when the dose was changed it disappeared, but the fact is, it was clearly related and she actually experimented with the dosage and found that she could almost predict the suicidal effects.

JOFRE: When Graham Aldred's wife was prescribed Seroxat 3 years ago she was depressed and anxious but not suicidal. Rhona Aldred was initially worried about taking an antidepressant. Her husband reassured her.

GRAHAM ALDRED

When Rhona brought the drug home, she said to me she had some reservations about it, and I said "Don't be silly, this is England, this is a country where you can trust medical regulation." Now she was right and I was wrong.

JOFRE: Shortly after starting on Seroxat Rhona became very restless, agitated and had terrible nightmares. After 11 days of mental turmoil she drove to a secluded country lane and killed herself.

ALDRED: This is what the regulator doesn't seem to understand, that there are people on the end of all this, there are people whose lives should have continued, there are people whose wife, whose sister, whose mother, whose children even, should be alive now and happily functioning in the family.

RICHARD BROOK

Expert Working Group May 2003-March 2004

When people take Seroxat they don't know what the implications are and they don't know if they're one of these people that maybe so adversely affected by this drug. And of course if they are, and they don't recognise it, and it doesn't work for them, then in a sense it's just like Russian roulette, they risk pulling the trigger, the bullet being in the barrel and it going off, and I think that's the reality of the situation, and I don't think the regulator sees it that way at all which makes it double risky.

JOFRE: The MHRA's responsibility for making sure drugs are safe doesn't end once they're licensed. It's also supposed to monitor their safety when they're on the market and widely used.

BRECKENRIDGE: It's very important that since safety is an issue which is built up as more experience is gained with the drug, that safety is kept under review and this is why we insist on post marketing surveillance of a drug, which means that its safety is kept under review during its lifetime.

JOFRE: The way the regulator has kept Seroxat safety under review though has raised concerns that were supposed to have been resolved 40 years ago, after a scandal where thousands of women took a drug that hadn't been properly tested and gave birth to babies that were deformed, that drug was called Thalidomide.

[Footage of thalidomide toddlers]

Their mothers took Thalidomide to prevent morning sickness, as a result of the tragedy that followed, an early warning system was set up that's called the 'Yellow Card Scheme' if doctors suspect a drug has caused a serious side effect they're supposed to report it to the MHRA on a yellow card. In our last programme we exposed serious flaws in the Yellow Card Scheme, two experts who appeared on that programme, asked the regulator afterwards to show them all the Yellow Card reports gathered on Seroxat. Normally secrecy rules prevent access to this data, so they were astonished when the answer was 'yes'.

CHARLES MEDAWAR

Author "Medicines Out of Control?"

We jumped up and down with glee, we thought this is the first time that any such analysis had ever been done, and of course at the back of our minds was the feeling that we were not only now in a position to evaluate how well the regulators had understood the problem of Seroxat, but also how good the Yellow Card system was.

JOFRE: They were given unprecedented access to every single reported side effect ever lodged about Seroxat, and it's one of the most complained about drugs in the schemes history. These were reports that were supposedly scrutinised during each of the previous safety reviews.

MEDAWAR: It hadn't been properly analysed, it hadn't been properly followed up, it was full of the kind of jargon that obfuscated meaning, it made things very unclear and uncertain, and it would be hard to imagine a sort of less helpful construction of the data that there was.

Dr ANDREW HERXHEIMER

Emeritus Fellow, Cochrane Centre Oxford

MAN: What amazed me was the haphazardness of it, for some things there was a lot of detail, for other things there was nothing, and it took a long while to make sense of it.

JOFRE: They found 91 Yellow Card reports from doctors who suspected Seroxat had prompted their patients to become suicidal, to self harm or to kill themselves.

[Yellow Card Report]

He clearly stated that he had not thought about suicide until taking Seroxat.

WOMAN: Even when a report ran only to one line, there was often little evidence it had been investigated further by regulatory staff.

[Yellow Card Report]

A patient shot himself a few days after starting medication.

MEDAWAR: You think for heavens sake, I mean what is happening? Is this an extraordinary callous doctor reporting, you know, on a tragic event with indifference or actually isn't what the doctor is saying is: "Here's the reason to come and see me, this needs to be followed up."

[Yellow Card Report]

We have evidence that the suspect drug drove patient to suicide.

Prof Sir ALASDAIR BRECKENRIDGE

Chair, Medicines Healthcare and
products Regulatory Agency

When information like this comes in this is investigated. The way that we.. we firstly we investigate

individual reports and then we take..

JOFRE: And how do you do that, you go back to the doctor and follow it up?

BRECKENRIDGE: Yes.. yes.

JOFRE: And that happened in all of these cases?

BRECKENRIDGE: Not in all of them at.. in the appropriate.. in the appropriate cases, this is.. these patients are followed up. The follow up rate for Yellow Card reports is some 48% - 49%.

JOFRE: The MHRA says that all suicides have now been followed up, if not straightaway, then as part of the current safety review. But what about the previous safety reviews, why didn't they investigate every reported suicide then?

CHARLES MEDAWAR

Author "Medicines Out of Control?"

These people, working in secret, had assured the public, through Ministers, that they had done three investigations into this particular problem, suicidality, and each time the drug came out with a clean bill of health, and they were not warranted.. I mean they were absolutely not justified in drawing that conclusion.

JOFRE: Not only has the regulator failed to follow up some signals that suggests Seroxat has driven some patients to suicide, the research has uncovered something else in the Yellow Card reports, another potential risk that hadn't been identified by the regulator, evidence that suggests the risk of suicide could be closely related to changes in dose.

[Yellow Card Report]

Dose increased from 10mg after two weeks on treatment. On the fourth day of starting the 20mg dose patient committed suicide by hanging himself.

Dr ANDREW HERXHEIMER

Emeritus Fellow, Cochrane Centre, Oxford

Half of the suicide reports that we looked at were associated with some change in dosage, either when the drug had first been started, when the drug was building up in the body in the first few days or after a dose change had occurred - either an increase or a decrease in dose - so that was the relationship which hadn't been spotted before.

[Yellow Card Report]

Patient committed suicide after having increased dose from 20mg to 30mg.

JOFRE: On the day that Adrian Keegan died, he told friends he'd taken three 20mg tablets of Seroxat

instead of the usual one in the hope it would make him feel better. His parents now believe that's why he hung himself.

CHRIS & DAWN KEEGAN

That is what's happened to Adrian.. Adrian has increased his dosage, now some might say he did it himself, but if he had have known he wouldn't have done it - so the increase of dosage killed Adrian.

JOFRE: Advice to doctors has always been that depressed patients should be started on 20mg of Seroxat, in practise the dosage is often increased. But last October the Expert Working Group discovered something shocking; firstly there's no evidence that Seroxat actually works any better above 20 milligrams for depression, but secondly, rapid increases in dose are much more likely to cause serious side effect. This was spotted, according to the MHRA, after staff took a more rigorous approach to clinical trial data they'd had for 15 years.

RICHARD BROOK

Expert Working Group May 2003-March 2004

They looked at the data and discovered that the data they had from that original submission indicated that Seroxat had little benefit above a 20mg dosage. And the side effects, particularly around withdrawal, increased quite dramatically post 20mg.

JOFRE: As the patients representative on the Expert Working Group Richard Brook felt this information should be released straightaway, but for four months nothing happened. Eventually he told the MHRA that if they wouldn't tell patients he would even though he could be breaking the law.

BROOK: It's one of those moments where you have to say: "Actually if I don't do this I can't really live with my own conscience and my own views."

JOFRE: Although he was trying to help patients, the MHRA threatened Richard Brook with legal action. A letter from the Chief Executive warned he could be prosecuted if he published the new dosage information about Seroxat.

BROOK: Clearly, it's got huge implications, I mean, you know, clearly it potentially is around my job, my livelihood, my reputation, my career, it affects my family, my daughters, my wife so huge.. huge implications, it wasn't like this is something you'd do lightly.

JOFRE: In the end, Richard Brook got his way the regulator wrote to doctors about the groups findings, curiously though, this crucial new information was presented as a reminder.

BROOK: It lacked honesty, what they actually did was say: "After extensive review, we have discovered this is a reminder we ought to give to people." That was absurd, I mean the information had been around, the MHRA just didn't admit to the fact that either they'd missed it or even worse, they hadn't actually bothered to tell people.

Prof Sir ALASDAIR BRECKENRIDGE
Chair, Medicines Healthcare and
products Regulatory Agency

There was a difference in views as to whether the agency had sat on information, and Richard felt I think that the agency had sat on information on dose, and we were quite clear.. the agency is quite clear it had not sat on information on dose.

JOFRE: You're not quite getting Richard Brook's point are you, that patients need to know this information as soon as it becomes available, it's their health.

BRECKENRIDGE: It is a matter of regulatory and practical judgement as to when information should be transmitted. When it is in the public's interest that information should be transmitted rapidly, we will do it.

JOFRE: For Richard Brook the MHRA's attempt to gag him was the final straw, he resigned from the Expert Working Group the day after the dosage information was finally released.

BROOK: I have regrets it didn't get it out as clearly as I think it should do, and I have regrets it hasn't yet pushed the regulator to understand that it needs to change its processes and its approach to regulation, but I hope those things will come. So it's a decision I don't regret, but I didn't find easy and I still don't find easy thinking about it.

JOFRE: Do you regret the fact that Richard Brook was threatened with legal action for revealing any of this?

BRECKENRIDGE: That was.. that was unfortunate, I regret Richard leaving the committee because he was a very valuable member of the Expert Working Group and we certainly hope to maintain contacts with Richard and to obtain the benefit of his advice.

JOFRE: The controversy surrounding Seroxat hasn't stopped it becoming the most profitable drug that GlaxoSmithKline has ever made. Just six years after launch it became the company's first billion dollar product, a triumph some believe of marketing over science.

Prof PETER TYRER
Head of Psychological Medicine
Imperial College

For a time, even only in a matter of a few years, almost critical scepticism, the objectivity were suspended in favour of the all out rush to develop these new drugs and develop new markets.

JOFRE: Because there was such an excitement created about them.

TYRER: Yes, as the head of GlaxoSmithKline once said: “There’s a lot of runway space out there for Seroxat you know, let’s get the planes down.”

JOFRE: Getting the planes down, would the company hoped, lead to their second billion. It applied to extend Seroxat’s licence for the treatment of five more illnesses, some familiar like obsessive compulsive disorder, some not so familiar like social phobia. Each of Glaxo’s planes landed safely with the regulator’s full approval. As more and more people are being prescribed Seroxat for a bewildering array of illnesses, another massive problem has emerged, a problem not as devastating as suicide, but one that affects a much larger number of patients, many people on the drug say they’ve become hooked. Again, the regulator has failed to issue proper warnings, even though the evidence has been staring them in the face for years. When Seroxat was first licensed it was marketed with the regulator’s approval as a safe non addictive drug, back then even Dr Healy believed the hype.

Dr DAVID HEALY

Director

North Wales Department of Psychological Medicine

When the drugs came out first I had absolutely no concerns at all that there might be withdrawal problems

with the pills. I think probably like almost all clinical psychiatrists here in the UK, I would have actively reassured people that they could go on these drugs without any risk of withdrawal at all, that this group of

drugs was very, very different to drugs like Valium and Librium that had actually gone before them, to which people could get hooked.

JOFRE: That’s what Sarah Venn was told, she was prescribed Seroxat for dizziness seven years ago, but whenever she tries to come off it the withdrawal symptoms just knock her sideways.

SARAH VENN

If I forget to take my pill for just one day, by the afternoon I’ve started to run a fever, then my vision gets blurry and I see objects sort of moving around the room. I look like I’m having fits and spasms and I get incredibly depressed and I have never been depressed before, and it’s ironic that I’m taking an antidepressant and it’s made me suicidal on occasions.

JOFRE: In the late 1980s, before Seroxat was licensed, GlaxoSmithKline funded a clinical trial into the drugs affects on depressed patients. The man they asked to conduct it was Professor Peter Tyrer a world expert on drug dependence. He came across a problem that would go on to affect millions of patients around the world. After six weeks on Seroxat some of his patients were feeling better, but some of them were also hooked.

Prof PETER TYRER

Head of Psychological Medicine

Imperial College

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

JOFRE: As far as you were concerned then were these people dependant on Seroxat?

TYRER: They were showing yes signs of dependence...

JOFRE: And this was after..

TYRER: ..after only six weeks.

JOFRE: ...just six weeks on the drug.

TYRER: Yes.

JOFRE: Some of the withdrawal effects were very disturbing.

TYRER: They also felt more anxious, they felt this feeling of dysphoria, the feeling of being depressed and in some cases entertaining suicidal thoughts.

JOFRE: That sounds pretty serious then if people were thinking of suicide when they stopped.

TYRER: Yes it is serious and in particular we were led to believe that these drugs were particularly effective against suicidal thoughts and therefore, having them at any stage during the course of treatment...and on withdrawal was a matter of great concern.

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

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

JOFRE: And as far as you're aware they didn't investigate the problem.

TYRER: No.

JOFRE: We asked GlaxoSmithKline if further studies were commissioned as a result of Professor Tyrer's findings on withdrawal. They didn't say. What they did tell us was 'The company reviewed reports of such symptoms in all its clinical trials as a matter of course'. If the drug company didn't investigate it, what about the regulator? Since the early 90s its Yellow Card scheme has been throwing out signals that

many patients are hooked on Seroxat, the drug has attracted more Yellow Card complaints about withdrawal problems than any other prescription medicine. The MHRA says: "Patients should have been well aware of the risks before they started taking it."

Prof Sir ALASDAIR BRECKENRIDGE
Chair, Medicines Healthcare and
Products Regulator Agency

They were warned from the time the drug was licensed that there was a risk of withdrawal. This has been mentioned in every review, every publication coming from the Committee in Safety of Medicines, the problem of withdrawal, that has been publicised in patient information leaflets that there is a problem with withdrawal.

JOFRE: Really, up until last year the patient leaflet said that withdrawal symptoms were "not common" and "you cannot become addicted to Seroxat". The leaflets wording was approved by the regulator.

So was it helpful to tell patients that they couldn't become addicted to Seroxat?

TYRER: No it wasn't.

JOFRE: What do you think patients would have understood by that?

TYRER: Well they would have understood that it wasn't habit forming and that really when the time came for them to stop their drugs they would have no problem in stopping them, and clearly, the evidence didn't support that.

JOFRE: Do you think the regulator should have insisted on something clearer in the patient information leaflet?

TYRER: Yes.

SARAH VENN

I am absolutely fuming that this drug was allowed to be put on the market with completely misleading information that people like me were taking it, believing what we were told, doctors believing what they were being told. There is no reason why I should be sitting here today in the state that I am because the regulators knew about this problem. GlaxoSmithKline knew about this problem, but they did nothing and they have changed the course of my life and thousands of other lives.

RICHARD BROOK

Expert Working Group May 2003-March 2004

It was clear from the information, that certainly I saw, that the original trial data showed there were quite severe withdrawal issues. It was clear the studies were not done as well as they could be done compared to modern day standards, but ultimately there was no mistaking, there was a very clear issue

that withdrawal really affected people particularly at higher dosages and at long periods of using the drug. And that information has been in the vaults of the MHRA for over a decade and known to the manufacturer indeed for over a decade.

JOFRE: In June last year the leaflet underwent a dramatic transformation, the claim that you cannot become addicted to Seroxat was removed and startling new statistics about the frequency of withdrawal affects were added. Out of the blue patients were told that one in four people could now experience withdrawal problems, some of them very severe indeed, so why did a proper warning come 12 years after the drug was first licensed?

BRECKENRIDGE: It takes time for clinical trial evidence to become available.

JOFRE: It takes 12 years to find out that a quarter of people taking one of the most widely prescribed antidepressants will suffer withdrawal problems.

BRECKENRIDGE: The problem of withdrawal..

JOFRE: Is that your position?

BRECKENRIDGE: The problem of withdrawal was highlighted early on. We were unable to give precise figures, as time has gone on...

JOFRE: Why were you unable to.. you're supposed to protect the public, you're supposed to listen to the public, why were you unable to give a figure?

BRECKENRIDGE: Because we did not have reliable information available to us on which to base advice on figures.

JOFRE: GlaxoSmithKline says it gave the regulator the results of some clinical trials in the year 2000, it was from these that the one in four figure was drawn and added to the patient leaflet three years later. However, neither the company nor the MHRA will tell us when these studies were originally carried out.

CHARLES MEDAWAR

Author "Medicines Out of Control?"

The regulator should be covered in shame to admit that they had failed to spot an adverse effect which people had been sounding off about on the internet in.. by their thousands and thousands, and suddenly to admit that this side effect is real after all and that it affects a quarter of all users. The regulator should be deeply ashamed.

Prof Sir ALASDAIR BRECKENRIDGE

Chair, Medicines Healthcare and products Regulatory Agency

There is no other agency which has kept these.. these drugs under such constant and careful review since 1990 as we have done and we will continue to do so in the interests of the public health.

JOFRE: For years patients and their families have tried to tell the regulator about dependence, about self harm, about the risk to children, about the risk of suicide and for years they've been ignored.

Do you trust the regulator?

CHRIS & DAWN KEEGAN

DAWN: No not any more, no I don't.

CHRIS: How can you trust them? You know, when someone in that.. as much authority as they've got, they're supposed to be looking after everybody in the country is lying about the information that they've got, you cannot trust them, it's impossible to trust them.

JOFRE: Without trust we can't be sure we're being told everything about the medicines we take.

RICHARD BROOK

Chief Executive, Mind

I think this is actually an issue that probably goes beyond Seroxat and I find it hard not to believe there aren't other drugs that might be in the same category as Seroxat, that have lacked that robust clear analysis that's allowed us to make a decision about how they should be used, what information people need before they use them - so I actually think this is a major issue for us in the UK.

JOFRE: Do you think this whole episode has wider implications, it's not just about Seroxat or antidepressants?

Dr MIKE SHOOTER

President, Royal College of Psychiatrists

Oh no it has huge implications, I think once again we're seeing the SSRI's being the focus for something much wider in psychiatry and we're seeing psychiatry being the focus for something much.. much wider in medicine as a whole. I think, you know, a few years down the line we're going to be talking about this with many more sorts of medication than psychotropic medication.

JOFRE: So you think this has ramifications right through medicine as a whole.

SHOOTER: Right through medicine.. right through medicine.

JOFRE: There's no doubt Seroxat helps many people, but what about those who have been harmed, it was the regulator's job to protect them. Its failure to do so must raise serious concerns about whether the regulator's advice on other prescription medicines can be taken on trust.

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