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THE ATTACHED TRANSCRIPT WAS TYPED FROM A RECORDING AND NOT COPIED FROM AN ORIGINAL SCRIPT. BECAUSE OF THE RISK OF MISHEARING AND THE DIFFICULTY IN SOME CASES OF IDENTIFYING INDIVIDUAL SPEAKERS, THE BBC CANNOT VOUCH FOR ITS COMPLETE ACCURACY.

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#### ACTUALITY OUTSIDE ASTRA ZENECA

ALEXANDER: I’m standing outside AstraZeneca’s global research and development offices in Cheshire. They’re one of Britain’s biggest pharmaceutical companies, employing 65,000 people around the world, and last year made over \$31 billion in worldwide sales. They’re now facing thousands of legal cases in American courts over claims they failed to adequately warn people of risks associated with one of their blockbuster drugs.

SCOTT: I put something in my mouth that is causing me problems for the rest of my life and I’m angry about that, because it was a pill.

ALEXANDER: Tonight File on 4 investigates claims that a drug that’s been prescribed to millions of patients has severe side effects. We hear from a company insider about the pressures to bury bad news when the drug was being launched, and we ask whether drug companies should tell us more about the medicines we take.

SIGNATURE TUNE



SCOTT: I have peripheral neuropathy, which it affects my fingers and my hands; I have poor eyesight; I like to laugh and make fun of it, but I am forty years old and I walk with a walker, so that's horrible. I'm sorry.

ALEXANDER: Don't worry, okay.

SCOTT: And how it affects my hands and legs, it really limits me on what I can do.

ALEXANDER: Charla is one of over 14,000 people suing AstraZeneca in the American courts, alleging that the pharmaceutical company downplayed the drug's links to excessive weight gain and diabetes and marketed it for treatment of conditions for which it hadn't been approved.

NATIONS: In the state litigation, they are primarily New York, where we have about close to 12,000 cases on file. Then there's litigation in New Jersey in State Court, there's litigation in Delaware State Court, and in Orlando, which is the MDL, the Multi District Litigation, the count there is approximately 6,500 to 7,500 cases.

ALEXANDER: Howard Nations is one of the lawyers involved in the legal action. He represents 3,500 people suing the company and claims there's evidence which points to a link between Seroquel and putting on weight.

NATIONS: The taking of Seroquel, in a large number of patients, will result in attacks on the neurons in the brain, which leads to a ravenous appetite. The ravenous appetite leads to just uncontrollable eating, which leads to weight gain and then the development of diabetes. The most extreme case I have is one where a lady weighed 108lb, that was her normal weight and had been for years, she was 51 years old, and she gained 200lb over a six to eight month period.

ALEXANDER: What's alleged is that AstraZeneca knew of the risks of weight gain when Seroquel was first licensed. There was a reference to weight gain in information about possible adverse reactions, but the lawyers argue that this was "buried" and they "downplayed" the level of risk shown in the company's own trials. They say it should have been clearly displayed for patients like Charla.

SCOTT: I'm angry because I'm such a stickler for details and I read everything and, you know, I want to know what's going in my body, and there was no, nothing telling us 'oh don't take this because because because ...' If it was, I would have never taken it, because it has affected how I raise my children, how I live my life, what things I can do, where I can go. I can hardly go outside sometimes, I can hardly get out of my bed sometimes; my body won't allow me to do that and I'm angry about that, because it was a pill.

ALEXANDER: AstraZeneca has since changed the Seroquel labelling and there is now a more prominent warning about high blood sugar and diabetes. The company would not be interviewed for this programme. In a written statement they say Seroquel is an important medicine and its safety and efficacy has been evaluated in clinical trials with thousands of patients. They say the evidence didn't back up the claims that Seroquel was responsible for the alleged injuries, and they went on:

READER IN STUDIO: When Seroquel was first approved in the US, the label alerted physicians that diabetes mellitus, hyperglycaemia and weight gain had been observed in clinical trials. We have continued to update the label on these topics as the science has developed. Diabetes is a very common disease and the type of diabetes at issue in these cases typically develops over a period of ten to twelve years. It's difficult to determine why a particular individual developed the disease.

ALEXANDER: It is clear from internal emails and unpublished studies which have come to light because of the legal action, that AstraZeneca were indeed concerned about the issue of weight gain. In one such email, written in 1997, immediately prior to the product launch, a Seroquel Project Physician, Lisa Arvanitis, noted how it had been observed across all their trials. She wrote:

READER IN STUDIO: I was really struck by how consistent the data was.

ALEXANDER: And she went on to describe how weight gain was more rapid initially, slowed but didn't stop over the longer term, and that the proportion of patients with clinically significant weight gain after a year was 45%.

READER IN STUDIO: This was quite surprising to me - not the weight gain, but the consistency.

ALEXANDER: But this was very different to the message that was being promoted to some patients.

#### ACTUALITY IN CHICAGO

MAN: ... got a little change for a cup of coffee?

MAN 2: Yeah.

ALEXANDER: The Central Plaza Residential Nursing Home on the west side of Chicago, one of the roughest districts in the country. It's a faceless nondescript building, four storeys high. The two or three hundred people who live here have nowhere else to go; they are mentally ill and many have been discharged here straight from prison. People wandering aimlessly in and out are hardly dressed warmly in spite of the freezing cold weather. The psychiatric director here and at twelve other similar homes is Dr Michael Reinstein, who claimed to be one of the biggest prescribers of Seroquel in the world.

ROE: There's nobody quite like Dr Reinstein, not here, not maybe anywhere in the country. He gives more of these psychotropic drugs like Seroquel than just about anyone. Over a ten year period he's written more than 40,000 prescriptions of Seroquel; at the same time he's received \$500,000 from the company.

ALEXANDER: Sam Roe, a journalist at the Chicago Tribune, has investigated Dr Reinstein and his relationship with AstraZeneca. The money Dr Reinstein received from the company wasn't, in fact, for his massive prescribing of the drug, but for promoting it. They used him as a so-called Key Opinion Leader and he made over five hundred presentations about Seroquel in a ten year period. And in one sales brochure, which lawyers say was circulated to doctors by AstraZeneca, far from warning of the risks of weight gain and diabetes, he explicitly said the drug could have positive benefits.

READER IN STUDIO:                    We have found Seroquel to be ideal in patients who have problems with weight gain and, due to this, the development of diabetes. In our experience, weight gain is not an issue with Seroquel, unlike some other antipsychotic medications.

ROE:                                        He was travelling the country promoting it as a wonder drug, not only for schizophrenia, but it also had this unintended yet welcome side effect, that some people would lose weight. And so he would go around and tell people that yes, some people are losing weight on this drug, and in fact he would mention at some locations that we've had nurses, he would say, at nursing homes ask me about the drug because they themselves wanted to lose weight. He's a real opinion leader, as they call it in the game; he's out there talking to thousands of other doctors and telling them how great certain drugs are. And so he's been valuable to that company, there's no doubt about that.

#### ACTUALITY OF GOSPEL MUSIC IN CHURCH

ALEXANDER:                            Sunday morning in the Christ Centre of Truth Church, a small prefabricated building next to a fast food takeaway in a run down area on the south side of Chicago.

#### MUSIC

ALEXANDER:                            Among the congregation is Chanille Hayes, who became a patient of Dr Reinstein after suffering a nervous breakdown nearly ten years ago.

HAYES:                                    I started picking the weight up, picking the weight up, then I was asking Dr Reinstein, you know, is there something, you know, that you can give me to help me lose the weight, and, you know, his answer was, 'Oh Miss Hayes, don't worry about it, Seroquel will help you lose weight,' and my thing was, because he's a plus sized man himself, I couldn't understand why he wasn't taking it. I just listened to what he told me and continued to take Seroquel and I would probably, you know, start losing the weight, so that's what I did.

ALEXANDER:                            And did you start losing the weight?

HAYES: No, actually I gained more weight.

ALEXANDER: Chanille, who is 37 years old, says she has developed diabetes since taking Seroquel and claims her weight has shot up to more than twenty stone within two years. As a result of this huge weight gain, she suffers from sleep apnoea - a condition which severely affects her breathing - and she has to attach herself to an oxygen machine every night.

HAYES: This is a, they call it a CPAP machine. So what I have to do is wear this. Well, it goes over my head and the oxygen comes out and that's how I have to sleep at night. I get tired or, you know, my legs, and the amount of weight, sometimes my back hurts. I tried not to let it get me down as much. I think if I could just lose the weight then I probably wouldn't need the medicine. But I know if I never would have gained the weight, I wouldn't be on it anyway. So it's like everything is like if I could just lose the weight.

ALEXANDER: Lawyers focus on the role played by Dr Reinstein. In particular they point to a study he and his colleagues carried out which, according to him, showed that Seroquel actually helped patients to lose weight. According to the study, all 65 patients who had Seroquel added to their drug regime showed statistically significant weight loss. In their statement to File on 4, AstraZeneca say they didn't sponsor this study, they only provided the drugs, but lawyers claim the results were adopted and embraced by the company to help promote the drug to doctors. David Matthews is a lawyer based in Houston, who also acts for several hundred people suing AstraZeneca.

MATTHEWS: The epidemiological probability or possibility within any study where 100% of patients would lose weight on a drug that has a class effect, a known class effect for over a decade to cause weight gain and abnormal metabolic function is simply absurd to me. I think that in order to show the doctors and the world out there, at least in the United States, that, you know, our drug isn't a problem, AstraZeneca then really adopted this study that Reinstein did that said that in fact all these patients lost weight; it was almost a miracle. And what we saw, I think, back in the time when Reinstein finished his study, was they were going to take that study and use that study with other doctors, and they did that. They had multiple ways to know that their drug caused weight gain and diabetes



READER cont: suggesting we kowtow to his whims, nor to support any unethical behaviour. I am suggesting that if he has a conflict over trial protocols or personnel, we need to be more responsive to his opinions and needs.

ALEXANDER: And he went on:

READER IN STUDIO: It seems we are annoying possibly our most important single customer and that is not acceptable. This issue has been going on for quite some time; my concern is that Dr Reinstein will be looking for a trigger to leave our fold. That would be disastrous for our Seroquel business in the short and long term.

ALEXANDER: In spite of these concerns, Dr Reinstein continued to be paid as a speaker by AstraZeneca for another seven years until 2008. In total, he earned nearly half a million dollars from the company. Dr Reinstein wouldn't be interviewed for File on 4, but in a statement his lawyer told us the Seroquel study had been a pilot and he had advised that a fuller study should be carried out. He insisted:

READER IN STUDIO: Dr Reinstein has never told any patient they should take Seroquel to lose weight. Payments do not and did not influence his prescribing.

ALEXANDER: We would like to have spoken to AstraZeneca about their relationship with Dr Reinstein, but again they refused to be interviewed. In a statement they said:

READER IN STUDIO: AstraZeneca is committed to providing doctors with accurate information about its medications and the illnesses they are approved to treat. One of the ways AstraZeneca provides that information in the US is through a speakers programme, in which recognised medical experts present information on the relevant illnesses and the ways AstraZeneca's medications may help in treating them. The speakers are selected on the basis of their expertise and are compensated according to the fair market value for their time.

ALEXANDER: Before it was marketed in the United States, Seroquel had been launched in the UK, and here too the tensions were evident between clinicians and those marketing the drug. John Blenkinsop was the medical advisor for AstraZeneca's UK operation. It was his job to ensure that any promotional materials used here were accurate and were supported by medical evidence. Speaking publicly for the first time, he's told File on 4 how he came under pressure from the marketing team.

BLENKINSOP: They came at me with a number of potential claims, all of which were trying to intimate that Seroquel was not associated with weight gain. They either wanted to say that there was no weight gain or that the weight gain was only for the short term. They came with a number of different attempts, none of which I would approve. The data pointed in the opposite direction.

ALEXANDER: And what was your reaction to that?

BLENKINSOP: Well, I understood where they were coming from. I had some robust discussions with them and exposed them to the data. That didn't seem to stop them, because they were desperate for a differential advantage over one of the competitor products, and they didn't have one. In the end I was put under quite a significant amount of pressure by the marketeers to sign off claims with regards to a lack of weight gain and I was unwilling to sign that off. The marketeers made it clear that this could be a career limiting step.

ALEXANDER: In the UK, Seroquel hasn't been marketed in medical journals on the basis of claims about weight, except for one advertisement which we've seen, which was published in April 2004 in the British Journal of Psychiatry. It claimed that Seroquel has - quote - "a favourable weight profile across the full dose range." John Blenkinsop, who left AstraZeneca three years after the launch of the drug, questions the difference between the marketing here and in the US.

BLENKINSOP: Well, I find it interesting that the claims that could be made in the US and the UK were different based upon the same body of data. From launch right through to the present day, with the exception of the April 2004 advertisement, as far as I can see no promotional claims were made about Seroquel and a favourable weight profile



MATTHEWS cont: indicated for and that is schizophrenia. And we have seen over the course of time that that's exactly what was happening with that drug, that they had it targeted to be used for a variety of behavioural problems from anxiety to depression, to ADHD, to lack of sleep - insomnia. They were sending out sales reps on a regular basis to push these drugs and this drug in particular for off-label uses.

ALEXANDER: Off-label use, where drugs are given to treat conditions beyond those for which they've been licensed, is perfectly legal if the doctor thinks it's appropriate. However, the drug company is not allowed to promote a drug for any off-label use. In their statement, AstraZeneca told us:

READER IN STUDIO: The document cited by plaintiffs' lawyers reflect the company's intent to explore additional indications for inclusion in the Seroquel label through our clinical development programme and to publish the results of the clinical trial as appropriate. The documents do not reflect any intent to violate AstraZeneca policy or applicable regulations through off-label promotion.

ALEXANDER: However, in the United States, the company has recently agreed to pay \$520 million in relation to two federal investigations and two whistleblower lawsuits over the sale and marketing of Seroquel. One of the investigations relates to illegal off-label promotion of the drug. In the UK, according to research group Datamonitor, 73% of prescriptions for Seroquel are for off-label use - for other illnesses including eating disorders and post traumatic stress disorder. Again, doctors are perfectly entitled to do this. But Dr Tim Kendall, who is responsible for drawing up guidelines on the use of anti-psychotics for NICE – the National Institute for Clinical Excellence - is concerned when this becomes widespread.

KENDALL: I would say that the correct way of using a drug off-label would be when you've exhausted other treatments that we know to be effective and are licensed and that they have not been effective, and I think then the choice of drug that you might consider would be based on having expert knowledge of the research around that drug.

ALEXANDER: In the case of Seroquel, something in excess of 70% of the prescribing of it is off-label. How do you feel about that percentage?

KENDALL: It's extraordinary. I would be very concerned about that, not only because it means that 70% of the use of the drug is without any real evidence to support it, but also how have we got to the point where a drug is being used off-license? That makes me concerned that there's someone encouraging that use, and I don't know who that would be, but it could be doctors, it could be drug company representatives, it could be others, and they shouldn't be doing that and I think they know that.

ALEXANDER: There is no evidence to suggest that Seroquel has been promoted for off-label use in the UK, however if a drug company were to illegally promoted its drugs here, the sanctions are markedly different from those in the US. There, the Food and Drugs Administration, the FDA, can impose huge fines. AstraZeneca was not the only company to be penalised last year. Eli Lilly paid \$1.4 billion over its marketing of Zyprexa, Seroquel's biggest rival, and Pfizer paid \$2.3 billion, mostly over its painkiller Bextra, which has since been withdrawn from the market. There is no such sanction in the UK. Here, the promotion of drugs is regulated by the ABPI, the Association of the British Pharmaceutical Industry. They wouldn't be interviewed for this programme. However, there is another, little known body, the Prescription Medicines Code of Practice Authority, which is responsible for enforcing the ABPI code of practice. Heather Simmonds of the PMCPA says self-regulation is sufficient.

SIMMONDS: Constitution and procedure doesn't include fines as a sanction, because the belief is that the publication of the detailed case report is a very powerful sanction and that will impinge on reputation.

ALEXANDER: But in America, for example, the FDA, who are performing a similar role to you, have the power to impose massive fines, and indeed in the last twelve months we've seen companies being fined many millions, and in some cases over a billion dollars. Why do you think that we don't we do that in this country?

SIMMONDS: I think the self regulatory system has decided that the means to demonstrate effective self regulation is to publish the detail on the particular cases. We publish more detail in the UK than in any other country, as far as I know. There are additional sanctions that can be used. The appeal board can impose things like a public



ALEXANDER: We showed the documents referring to the burying of trial data to Dr Tim Kendall, who's responsible for developing guidelines in mental health for NICE.

KENDALL: These emails are absolutely about marketing, marketing these drugs as if they were marketing a piece of technology. It really is utterly cynical about concealing data so that their market share isn't damaged. I think this is utterly unacceptable. What really horrifies me more than anything else is that anti psychotics are a treatment associated with quite severe side effects, which we only use, in the main, to help people who've got really very severe problems. And this group of people, people with schizophrenia and with bipolar disorder, are people who suffer probably more than most others throughout our society. And to mess about with the data around these drugs, about their usefulness, about their effectiveness, to mess about with that is unforgivable and they should be punished.

ALEXANDER: Again, AstraZeneca wouldn't be interviewed, but in their statement said:

READER IN STUDIO: Whether or not the results of a study were favourable to Seroquel and/or were published in a scientific journal, AstraZeneca provided safety data for Seroquel to regulatory authorities, including the FDA.

ALEXANDER: Under current laws, both in the United States and here, pharmaceutical companies are obliged to provide regulators with all their test results from all their trials, showing how well the medicine works and what its side effects are. They also have to provide periodic safety update reports after it's been licensed. However, this information will sometimes run to many thousands of pages, and Dr Fiona Godlee, editor of the British Medical Journal, says this has meant in other cases the system couldn't cope.

GODLEE: The regulators are in a position to ask for any data that they think is necessary. The problem is that the scale of what they're being asked to do is so huge, and we do have evidence that some companies play a sort of game in swamping the regulator with information, because one's talking about now truckloads of paperwork that might go alongside an application for one drug, and the Food and Drug Administration and



