# *Patient perspectives on informed drug prescribing*


## *Charles Medawar*

*Social Audit Ltd, UK*


Presentation to Medwatcher Japan and T*he Informed Prescriber*

Tokyo, 23 November 2004

Thank you very much Mrs. Minaguchi - and thank you all for coming to listen to what I have to say.

I'm coming to the end of, I'm afraid, a very short visit to Japan. This was my first visit and it has been the most extraordinary experience. I know that when I go home, my wife and my friends will casually ask, as one does when people come back from a trip abroad, "How was it in Japan?" I was thinking about that last night and I imagined myself saying, "Well, it was amazing, but I can't really say more unless you would like to make an appointment for maybe 3 hours, and then I can describe what an extraordinary experience it has been." The problem for me would be how to describe a square with six sides or a circle with rough edges. I use this surreal image to give you some sense of what I have felt being here, feeling completely at home and yet in a completely strange environment. I mention this because some of the things that I am going to say to you may make you feel rather the same. Be patient, forgive me. I am delighted to be here and am deeply grateful, especially to Dr. Hiro Beppu and Dr. Rokuro Hama for inviting me.

I thought I should start by telling you a little bit about the organization for which I work. It both *is* an organization and it isn't. The fact is that I work on my own within a small organisation (Social Audit Ltd), but I mainly operate through a network of other people, many in different countries. However, I am part of an organization to the extent that we are a charitable body that subject to very strict legal rules. I have directors, and therefore I have to explain and justify to them what I do, and because we are mainly funded by a Quaker foundation (www.jrct.org.uk), I also have to account to its trustees. So basically, I think I'm asking you to trust me, and make up your own mind, on the basis of what I have to say – and not because I am affiliated to any particular institution.

I do belong to an organization, but it is a strange sort of organization. Its main purpose, as I see it, is simply to ask questions – especially the kinds of question that don't get asked enough. To be realistic, when you are part of a very small non-governmental organisation (NGO), you often can't do much more than that. In that situation, the challenge is not to attempt to do the job yourself: the aim should be to try to get the people who should be doing the job to do it properly.

So, our job is to ask questions. Furthermore, we often ask what might seem naïve questions, but I think it important that we do – because sometimes, naïve and even childlike questions come uniquely to the point. The kinds of question I tend to ask, do involve some broad understanding of the subject – but are essentially the queries of an 'intelligent, ignorant layman'. Here's an example of a naïve question: Why is it that there has never been a public inquiry – not in the UK, and I believe not in Japan - into any serious drug problem, even when many people are known to have suffered or died? Why is that? If there is a train crash, of course there is an inquiry. If there is a major fire or accident, even an earthquake, you want to be able to plan and take precautions, and to stop the same problems happening again. You need an inquiry to examine what happened, and why it happened, and to establish what can be done. So, there's a naïve question for you, and quite a challenging one – and I'm still looking for the answer, I admit.

So I return to what kind of organization we are – and my next slide tries to explain. On the left you see a huge redwood pine tree, dwarfing a tiny car and the people standing below it. That is my model of the classic organization. It has roots, it has a trunk, it has branches and leaves, and I think this particular tree represents a very large, probably multinational corporation. Next to it, on the other side of the slide, you see a tiny tree, a bonsai tree, and that is close to my image of what Social Audit is. It has roots, and a trunk, branches, leaves and even flowers. That is the kind of organization that I work for. And that means that sometimes I feel a bit like this (next slide), a one-man band. But I'm not. As I have emphasized, I work as part of a network – one reason I'm here to today. Working with other people with broadly similar concerns produces all kinds of possibilities. The English have an expression, it allows you to "punch above your weight", a term used in boxing, that implies that a lightweight fighting a heavyweight.

But my work isn't about punching: it's about trying to get explanations for what happens. Surely the most basic right in a democracy is to be able to ask questions. You may not get answers - but then you should be asking more questions. That, it seems to me, is what democracy is about, when it works. In any democracy, in your country, in my country, and in any other country you can think of, people need to be asking questions about where we are going, about why we are going in certain directions, and to what effect. Constructive criticism helps democracy to work.

**A patient perspective?**

I've been asked to talk about patient perspectives. When I see the word "patient", the first thing I think of is "What kind of patient?" Partly because we have this model of "the expert" on one side, and "the patient" on the other, we tend to think of the patient as one person. But that surely isn't true. Patients have different needs, and experiences, different competencies, tastes, intelligence and understanding. I wonder if in Japan, as in England, it is often said that doctors make the worst patients? Doctors are very poor patients because they know too much. There is something to be learned from that too. 'Patients' are, in reality, as different as you or me.

There is another point worth making about this word, "patient". There is another word we use in English for "patient", an IN·val·id. The same word pronounced in a slightly different way is in·VAL·id. The same word means two different things. One is something that is worthless, without value, and the other is "a patient" – someone on the receiving end of medical treatment. So there is the classic model: a knowing expert, a wise and trained professional, caring person - and on the other hand, the helpless, ignorant patient. Clearly, these days, that is something of an exaggeration – but we are still slow to recognise that patients come in different shapes and sizes, and can't and shouldn't simply be categorised as if they were peas out of the same pod.

I want to make another point about what it is like to be a patient, and about the health of individual patients. The health of the individual, in my view, depends overwhelmingly on the health of the community. Now, I know that my health is my responsibility, and there is a lot that I can do to preserve and improve my own health. But

how do I know how to do that? Where do I learn not to smoke, or to take exercise, or to eat effectively and nutritiously? I learn that from the community. And what standards do I, as an individual, experience of the drug safety standards that are set by the regulators? By definition, I experience an average standard – much the same as for everyone else. So, the point I'm making is that the individual has everything to gain from higher community standards. This is something that becomes even more important as the world becomes more of a global entity. There is no one in this room who is not touched individually in their own lives by developments internationally. And, if only because community health is probably the best single indicator of peace, world health should be a concern, even for the individual patient.

**Informed drug prescribing**

What exactly is informed drug prescribing? Well, probably the first thing to say is that the average prescriber knows hugely more than the average patient about the drugs that are going to be used. That is not in question. Doctors spend a great a deal of time studying and have a much experience with drugs - and the same goes for pharmacists, and to some extent nurses, as well. They are bound to know much more than the average patient. But my central proposition today is that they also have a great deal to *learn* from patients, and that's what you saw in the *Panorama* film.

If I sometimes complain about the quality of drug prescribing, it is not to say that I think it is at all easy to prescribe in an informed way. Being an informed prescriber must be incredibly difficult. First, that is because the prescriber is very dependent on other people, the regulators, companies and their professional training for the understanding they have about the medicines they are going to use. And secondly, because the medicines they are going to use may have very varied effects for different patients. You just saw that with the Panorama film. You saw some people saying that the drug paroxetine (Paxil/Seroxat) had been wonderful, and had actually saved their lives - and you see other people saying that it nearly ended their lives. This is a very unpredictable drug. I think like many things in life, it works as if on a bell curve (normal distribution). A few people do extremely well on the drug; a few people suffer quite a lot,

sometimes disastrously, on the drug - and in the middle, are a great many people who probably would have got on just as well without the drug as they did with it.

One of the things that started me working in this area was something that a pharmacist in a London hospital said to me once, and very much as an aside. He said, "It's interesting, even with these new anti-depressants, there is no evidence at all to suggest that the newer drugs are better than the older drugs, or even that there is any difference between the different anti-depressants." I went home and looked at my *Martindale's Extra Pharmacopoeia*, (an authoritative text), and I counted 80 different anti-depressants that have been introduced in Britain since the late 1950s. Extraordinarily, there is actually no measurable difference between the effectiveness of any of them, which clearly implies that they have a very non-specific effect. It also suggests that response to anti-depressants is equivalent to a very strong placebo effect, something that you, or certainly the professionals among you, will readily understand.

But as I said when I started talking, I am a layman and it is not for me to talk in too much detail about the drugs themselves. I want to talk instead, mainly about relationships. Why do I want to about relationships? Why don't I want to talk about molecules? Because I want to suggest that an understanding of drug safety and drug efficacy is not just to do with looking under a microscope or being an expert chemist, biochemist, immunologist or whatever. That is an important part of understanding what drugs do and how they work, but it is not the complete picture. My essential proposition is that *relationships* - notably between the public, professionals, business and government – actually make the difference between whether drugs are used wisely and well, or used excessively, insufficiently or just plain badly, as some drugs clearly are.

When thinking about such relationships, I often refer to an expression that my father first used – I found it in a book he wrote 30 or 40 years ago. I'm afraid I don't think it's translatable, but I will mention it anyway. The expression he used was "a conspiracy of goodwill". A conspiracy is a collaboration of people who usually have some bad intent, who usually want to do something wrong, like rob a bank. But "goodwill" introduces a contradiction into this idea.

What I think my father was saying as it applies to medicinal drugs (it's a pity he didn't elaborate on the idea too much), is that everybody wants to see drug benefits and

everybody wants to see drugs work well – and so we collaborate and invest, often quite unrealistically, in the belief that they do. In this process – the conspiracy of goodwill – we tend routinely to assume the best, and so lose sight of the thing that really matters, the relationship between drug benefits and harm.

Naturally, the patient wants to see drugs work well because they want to get better and to suffer less. Obviously, the doctor wants the drug to work well because it is good for the patient, it is good for medical practice and it is good all around. The doctor also knows that a strong placebo effect, the suggestion that the drug will work well, is a very important part of drug effectiveness. It is also clear that manufacturers want drugs to work well; of course they do, because it is their lifeblood. In fact, for doctors and for patients, and for pharmaceutical companies as well, the issue is the same: it's about survival. And the same is also true for government, for the regulators. The last thing a government wants is a drug disaster on its hands, because they assume much of the responsibility for drug safety, and may therefore be blamed if drug problems arise. This would be one of the reasons why safety and effectiveness of medicines is such a very secretive business. Trying to get information from the drug regulators, in my experience, is like trying to get blood from a stone.

Another point I want to make about relationships, and the importance of relationships in understanding drug safety and efficacy, is that expert chemists, biochemists or doctors are not necessarily experts at human relationships. To my mind, the importance of relationships underlines the importance of medicine as a democratic endeavour. I keep on using this word "democracy", because I envisage the patient as knowing more - or rather being allowed and encouraged to know more – and see this as essential, if people are to take a greater responsibility for their own health. But of course it means, sometimes, facing up to uncomfortable realities. Sometimes the drug will not work, and sometimes the drug will make you worse. The World Health Organization put out a press release last month suggesting that 10% of all hospital admissions were due to the ill effects of treatment, including notably, drug treatment. Patients need to take account of that.

I said that drug regulators tend to be a rather secretive lot, and I'll come back to that point. But this next slide is meant to explain my interest in the anti-depressant issue.

It actually began with involvement with benzodiazepine tranquilizers. In the mid-1980s, I became involved in an earlier *Panorama* program and also in a legal action relating to the risk of dependence on benzodiazepines. Benzodiazepines were first introduced in Britain in 1959, but it took 22 years for the first clinical study report to appear, with convincing evidence that withdrawal symptoms were a reality and a problem. Until about 1983, the drug regulators and prescribers rather assumed that people didn't suffer withdrawal symptoms (or that they were 'addiction-prone', if they did). If patients felt bad when they tried to stop taking the drug, the assumption was that this demonstrated that the drug was working all the time - and that if people felt anxious and ill when they stopped taking the drug, it simply meant that they needed to go on taking it. So doctors would tell the patient to go on taking the drug and, of course, the dependence problem would get worse.

I wrote a book about this in 1992, called "Power and Dependence", and it wasn't just about the benzodiazepines. I found the same thing had happened with the barbiturate drugs before the benzodiazepines, and with bromides before them, and with drugs like chloral hydrate, which was introduced into Britain in, I think, 1869. Indeed, it took 13 years for the first published report of addiction to heroin to appear after the introduction of this drug in 1902. So, there is a long history behind this 'therapeutic dependence' problem – and I'm afraid that the problem is with us still.

In 1994, I was asked to review a book called "Listening to Prozac", by this time, I had moved on to other things, I was not working on the benzodiazepine problem anymore. But when I did this review, I was astonished to find that there was all the evidence that the same thing was happening again, all the hallmarks of 'therapeutic dependence' and the same old explanations being given for it. The explanation was that when people stop taking Prozac, the reason they feel so bad is that the drug works so well, and so they need to go on taking it. There was no recognition of withdrawal symptoms at all in the official mind – indeed, the UK regulators have still not required companies to conduct controlled clinical trials to establish how great the problem is.

Following that review, I started to gather the evidence about 'therapeutic dependence' on antidepressants. It took time, but I was very much helped by evidence from the Internet. Believe me, the Internet is going change the history of medicine: it is going to give patients a voice that they have never had before. But even in the mid-1990s,

I began to find reports, from all over the world, of people describing what I could only understand as addiction to anti-depressants. They were saying, "I cannot get off this drug, and this is what happens when I try to do so." They would describe in detail, in their postings on the Internet, the symptoms that made them feel so bad. So, I ended up writing a long, 20,000-word monograph, which was then published in the *International Journal of Risk and Safety in Medicine*. Incidentally, I think it was a complete coincidence – I didn't know it at the time - but Dr. Hirokuni Beppu is on the editorial board of that journal, as he is on the editorial board of the *British Medical Journal*. Permit me to suggest this as a mark of the quality of both these journals, quite apart from underlining the importance of international collaboration.

**Risks in relation to benefit**

So, this paper was published in 1997, and the editor of that journal was also kind enough to allow to me to reproduce the 20,000-word document as the centrepiece of a website, which was launched early in 1998. The website – 'The Antidepressant Web' - is called 'ADWEB' for short, and I shall refer to it by that name. The idea of publishing this paper on a website was to invite comment, further information and peer review by professionals. I wasn't at this stage sure that I was right: I thought there was a problem, but I wanted to see what other professionals thought. So I put the thing up on the website and I waited, and waited, and waited, and waited … until the 21st century, by which time several things had happened … or not.

The first thing that didn't happen was any meeting to discuss the issues with the UK regulators. For six years, they refused to meet – and this explains why ADWEB displays facsimile copies of the several hundred letters we exchanged. The second thing that didn't happen was that, to this day, not a single professional has contributed to the discussion section on that website, which rather surprised and disappointed me, because by 2003, the website was getting about half a million visitors a year. What happened was the website was almost hijacked by patients. I couldn't cope with lots of patients writing in; I didn't design the website for patients. In fact, it's the worst designed website I've ever seen – I use it as a filing system. But patients just kept on writing in and saying,

"This is what happened to me", and others would then write in and say, "My God, yes, that's what's happening to me, too". And so a large body of data was formed.

The website was launched in early 1998, and its ultimate purpose was not only to find out about these SSRI antidepressant drugs, but to ask a wider question. The point of the website was not only to try to define what the problem was, but also *why* the problem was happening. Why did the so-called competent authorities apparently believe there was no problem? From my perspective, they have almost a monopoly of the relevant information and understanding - so, why did see no problem, and why were they apparently doing nothing? What was going on? What did they believe?

So, the website, ADWEB, in time developed as really quite a provocative tool. As you've seen from the *Panorama* program, there were two problems, one of which was severe withdrawal symptoms, which led to users feeling they were addicted. There happens to be an expert in this audience, Tokuo Yoshida, who can explain the meaning of dependence and addiction, and the significance of withdrawal symptoms, with far greater expertise than I can. But just for now, let's look at this just from the patient's perspective. If the patient feels real loss of autonomy, and says, "I cannot stop taking this drug", the patient feels addicted – even if the word, 'addicted', isn't quite the right term. It's not an approved or appropriate word, but that's the word patients use, and it describes something all of us understand. Certainly anybody who's ever habitually smoked, and quite a number of people, (an increasing number in Britain) who drink, will know what that means.

At this point, I think it appropriate to say something about this risk of withdrawal symptoms or dependence, in relation to the benefits of these drugs. The question of who needs anti-depressants, I think Dr. Beppu has already answered. Some people clearly benefit from them hugely. I think the people who get a really strong benefit are probably a small minority, just as it is a small minority who suffer badly - but there is no doubt at all that some people do need and benefit from anti-depressants. However, what we're seeing these days, not just with anti-depressants, but with cholesterol-lowering agents, drugs for osteoporosis and so on, is a pattern. The pattern is that a small number of patients really do benefit from these drugs. They are very important drugs for those few patients, but the need of the pharmaceutical companies to sell those drugs means that they

expand the market, essentially by changing the definitions of illness and of treatment needs. So, there are now, for example, I think over 340 officially defined types of 'depression' - and as anyone in clinical practice will appreciate, the SSRIs are quietly promoted for all kinds of clinical use, for treatment of all kinds of pain, to anticipate post-partum depression, pre-menstrual disorder, and so on. If only for the purposes of reimbursement, all of these states and more are not quite accurately described as 'depression'.

That means that these drugs are used by far wider populations than those who really need them, and that completely distorts understanding of benefit and risk. I mentioned the "conspiracy of goodwill", and now I return to the point. We all want drugs to work so much, that we come to believe they do, and so we distort understanding of the relationship between benefit and harm. We are all so hoping for benefit; thus we quietly overlook the element of risk. But risks increase with the numbers of people who use these drugs. So, if you prescribe a drug to somebody who really may not get much benefit - let's say the drug acts like a strong placebo - you are exposing them to the possibility of a slight benefit, but perhaps also to very significant risks.

**Antidepressant effectiveness**

Are newer drugs better than older ones? With anti-depressants, that was a very important question to ask because the first anti-depressants were introduced 30 years before Prozac was on the market. So how was Prozac going to make an impact on the market, if it was no better than other anti-depressants? It had to provide something special. The manufacturers needed to suggest that it was very much more effective than older antidepressants, if Prozac was to make its mark.

Now, you will remember I said earlier that I said there was actually no difference between any of the anti-depressants in terms of efficacy. I would bet that at least half of you are not too sure about that - but I think I can convince you that it's true with this little piece of, not evidence, but reasoning. If there were any one anti-depressant that really was more effective overall than any other, the publicity would have been enormous. The promotion would have been intense. The manufacturer of the better drug would have said, "Look! It's our drug, this is one to use." But you don't see that, do you? You just see

every manufacturer of anti-depressants saying, “Our drug is good”, and they point to one feature or another to demonstrate it. Of course all these drugs are ‘good’: there is no such thing as a second-best drug, because there’s no market for them. So they’re all ‘best’, but there is really not much difference between them. Different patients may respond individually, better to one drug than another, but that may have much more to do with dosage, circumstances or the half-life. Globally, there is precious little difference between these many different drugs.

How do anti-depressants work? Well, in Britain, and I suspect here in Japan, the story is the same. The suggestion is made that depression is, in fact, a serotonin-deficiency disease, and that by elevating the levels of serotonin and/or noradrenaline, somehow the body chemistry is restored to its natural levels. I’ll tell you how the term SSRI came into being. Five years after Prozac was introduced – and by then there was another leading anti-depressant called sertraline (Lustral is the brand name in England) as well - along came another similar drug, paroxetine (Paxil/Seroxat). The manufacturers of paroxetine would have been wondering at this stage, how to market their drug, when Prozac already had this dazzling reputation, and with sertraline dominant too. The manufacturers decided to exploit the idea (but in the absence of evidence therapeutic significance) that the high degree of serotonin reuptake inhibition by paroxetine made it more pure than the other drugs. So, it was SmithKline Beecham, as they then were, the manufacturers of Paxil, who coined this term SSRI - selective serotonin reuptake inhibitor - to somehow suggest that their drug was better than Prozac and Sertraline. There was no clinical evidence that this was so, but that was the marketing story and that was the story that stuck.

From a patient perspective, it was of course a very persuasive story – but a very unhealthy one too. One reason I think it’s unhealthy is because, if I went along to a doctor and said, “I am really depressed,” and the doctor said to me, “Ah, that is because your serotonin levels are low,” I would come away thinking, “Well, there’s nothing I can do, then…I don’t know how to fiddle with my brain chemistry.” I would become, in another sense, dependent on the drug, thinking that only the drug could help me, and believing that I couldn’t help myself or get help from family and friends. That seems a very poor model of health.

What is an effective anti-depressant? Let me explain the regulatory perspective. The Food and Drug Administration, the regulators in the United States, have a very specific requirement. They say that, to demonstrate that a drug is effective and to bring it onto the market, we want to see two clinical trials, in which you, the manufacturers, demonstrate that your drug is more effective than placebo. Well, anti-depressants aren't really very effective. You get some response to active drug is about 60% of users, while the placebo response is about 40%. And if you use a strong placebo, an active placebo, (for example, a dummy pill with a trace atropine, enough to dry the mouth to make the user think that something is happening), there's apparently no measurable improvement at all. A fairly recent review by the Cochrane collaboration established this: there is no measurable difference in the efficacy of an active placebo and the drug.

And this explains why the manufacturers of anti-depressants routinely conduct eight placebo-controlled studies, in the hope of getting two with positive results. Naturally, the manufacturers are less likely to publish the negative results, and extraordinarily the regulators allow this and don't judge efficacy on the basis of a meta-analysis of all the studies done. There is, in fact, one drug one the market in Europe called Reboxetine, where the manufacturers, Pharmacia/Pfizer, set out to get the drug licensed – but failed to get approval in the USA because of the eight placebo-controlled clinical studies they performed, only one produced positive results. That was good enough for the European regulators: the drug has been licensed since 1997, and is quite widely used in Europe, but it is still not licensed in the USA.

So here's another naïve question. Why are drugs licensed on this basis? I am, alas, flying home tomorrow. I'm going to get on an airplane, which I'm told, is safe and effective; I take for granted that it will get me from Tokyo to London (but accepting a minuscule risk this may not be so). Now, when I think that the plane is 'effective', I don't imagine that the plane will take off only once or twice in every eight attempts. I want to be sure of getting home. Why should drugs be different? When you buy a car, do you expect it to start once or twice every eight times you try to drive? It's absurd. But, if that's the reality, then let's live with the reality. Let's understand just what "effective" means. If it means, "sometimes very effective for some people", let's say so. Let's stop using this global term "effective", as if drugs always work and do no harm. You know, as

informed prescribers, even if many patients don't, that drug 'effectiveness' has everything to do with balancing benefit and potential harm. The lower the benefit goes, by definition, the greater the element of harm. So we need to think of efficacy, or effectiveness, as an integral part of thinking about drug safety.

How effective are drugs really? Well, my authority on this is Dr. Allen Roses, a distinguished geneticist who works for GlaxoSmithKline. He was quoted recently in a reputable newspaper in Britain, *The Independent*, and his estimate was that most drugs work in about half of the people who take them. See slide. To be fair to Dr Roses, he made this statement at a professional conference, and patients weren't meant to be there. But there was a reporter from this newspaper, and that is indeed what he said. The contrast between this reality and what patients actually believe will be obvious to you, whether you are a professional or a patient.

Dr. Roses then described, for each of several therapeutic areas, his estimate of the level of effectiveness of the different drugs. I won't discuss the figures in detail, but you will see (slide) here the reference to antidepressants – an estimated effectiveness of about 60% - from which you may subtract about 40%, which is placebo effect. So when you are thinking risk/benefit with anti-depressants, you need to think not only that perhaps 1 in 5 patients will benefit, but also about the welfare of the other four out of five. What kind of risk should they face, for the sake of those who do benefit? These are very difficult questions, but also very important ones - and they only underline how difficult it is to be an effective physician.

**Safety of drug users**

Let's turn to the question of how safe is safe. What does safety really mean? And here I want to go back to that central question raised in the *Panorama* film. How does the official or professional view of safety compare with the patient's view? And what do professionals have to learn about drug safety, as patients describe it? I want to illustrate this by reference to the second main problem with SSRI antidepressants, the risk of drug-induced suicidal behaviour.

One of the main points here is that the approved terms used in describing drug performance are often quite a long way away from the reality that patients experience.

One major problem here is that the commonplace and readily understood words that ordinary people use to describe drug effects – in this case, suicidality, suicidal ideation, suicidal thinking or suicidal behaviour – are not those you will find in reports of clinical trials. The 'official' word used for over a decade with anti-depressants, to describe the suicidal thinking found in clinical trials – is "emotional lability". But 'lability' just means an emotional volatility, and could just mean bursting into tears. If I suddenly started crying, you might say, "He's very labile." In other words, this is a very broad-spectrum term used to hide the specifics of what is happening.

Drug regulators and drug information processors are also obsessed with numbers. Of course, numbers have their uses – statistical treatments can be indispensble – but they're not the complete answer. Numbers can tell you some things, but they can't tell others. Imagine if you go to a football match and your friend says to you, "How was the football match?" and you say, "Oh, it was 2-1." He'd say, "Yeah, but how was the football match?" The score line, "2-1", is simply not an answer to that question. To that extent, the way in which the drug regulators focus on numbers is not helpful. The same is true also of some politicians, when they assume that, if there aren't enough numbers involved, there isn't a problem. Thalidomide was not considered a great problem in Japan because there were 'only' 300 people affected. But you only have to meet one of those people, to look at the question of adverse drug reactions in a completely different way. That is what happened to me a few days ago, seeing a presentation by just one of the 300 thalidomide victims in Japan. Mrs Yukari Masuyama is also here today: her presentation in Osaka was remarkable, and made the strongest impression on me; it is something that will live with me for the rest of my life.

Let's look more closely now at the official terminology used to describe suicidal behaviour. One signal of suicidal behaviour with these drugs is a very specific condition, described by the term, "akathisia". Literally (from its Latin origin), "akathisia" means the inability to sit down, total frenetic restlessness, you just feel so tense. That's "akathisia". But in clinical trial reports, it's often described in broad-spectrum terms, such as 'restlessness' or 'agitation'. The danger in using such terms is that you blunt the meaning – you don't illustrate what is happening and this is an important reason why serious adverse effects can get overlooked.

**Patient perspectives**

When you compare these official descriptions with what patients say, you get a very different picture. This quote (on the slide) comes from the wife of one of the patients in the *Panorama* film; she was describing her husband's terrible experiences with this drug. But I emphasize here, that this is not something that happens to everybody who takes the drug. This is a reaction that might only affect only 1 or 2%, a small number of the people who take the drug - though when you're talking about a drug that may be used by millions and millions of people, you're talking about a risk of tens of thousands of suicides. So numbers do matter - but words that reflect real life experience very much matter too. Here are some more descriptions of the kind you saw in the *Panorama* program. You can read them, and you can take them away in your handouts, so I won't read them again for you. The only point I want to make now is that patient reports can add essential perspective and colour and meaning. I think they have another value; they make the description more distinctive and memorable, they actually help you to understand and appreciate what an adverse reaction can mean in somebody's life.

Now let's look at the (next slide of) official descriptions and compare them with what patients had to say. These relate to the 'electric shock sensations' in the head, that people so often described in the *Panorama* film. The official description of these 181 Yellow Card reports, out of the total 1370, was 'paresthesia'. Earlier today, I discussed at some length with the conference organizers and with the interpreters, what this term, 'paresthesia' actually means. In short, it refers to a feeling of 'pins and needles', a sharp tingling under the skin - the most wonderfully imprecise description you could possibly give of the electric shock sensations in the head that users have so vividly described. Paroxetine users also mentioned something funny happening with their eyes - and this is how, in the English yellow cards (adverse drug reaction reports), these were described (see slide). What you see in this list is the patient experience reduced to a bland description of vaguely related symptoms - and the fragmentation of symptoms also means that you can't even begin to describe or understand the syndrome. You're just confronted with an abstract description of something called "abnormal eye movements".

The next slide is based on the terms that patients use to describe the same thing, and it shows us much more clearly what's going on. One of the users described it very

nicely here, saying: “If I turn my head my head through 90 degrees, my eyes take much longer, my eyes follow more slowly.” It’s like watching a film, ‘out of sync’, when the mouth movements are about half a second ahead/behind of the sound. It was the same thing happening with their eyes. That more detailed description would help a neurologist or a doctor to understand what was happening, much more than some reference to ‘abnormal eye movement’.

And this is not just some abstract point: when you get hundreds of reports like this, it isn’t enough just to classify them, using some vague and familiar description. You need instead to investigate them and to find out what is happening, but that is not what is generally done. Over the years, I’ve examined enough internal company documents to see that their main concern with such reports is not to investigate the causes and effects of the kinds of problems described here - but to investigate instead how to promote drugs, and to allay doctors’ concerns. Companies spend billions of dollars investigating what messages doctors respond to, and how different people respond to a particular message or advertisement – and that makes it seem all the more unacceptable that they don’t investigate, when they see reports of quite severe neurological manifestations associated with their drugs.

This next slide is one of several that make the same point, and a reminder of what happened with the benzodiazepines. “Every time I went to the doctor, and said there was a problem coming off the drug, the doctor said it was just my anxiety returning.” There really has to be some deep-rooted problem, when the same mistakes are happening again and again, over a period of more than a hundred years. Medicine really has got to change, and I’m suggesting that with the advent of the Internet, and greater democratization of medicine, it will change. However, the change we need is not going to happen unless you and your colleagues can lead this understanding. That’s why I’m delighted to be here to invite you to do this, and to spread the word among your colleagues and your fellow patients. The message is, that patients really do have a role to play in understanding how medicines work, and how they can work much better than they do.

**Evaluation of medicines**

At the moment, we assess drug safety and efficacy on the basis, overwhelmingly, of clinical trial results. That's what the regulators do: they assess the clinical trials that the companies conduct before the drug is licensed, and then they do some pharmacovigilance, some post-marketing surveillance. The main point I want to make here is related to these two different processes, pre-marketing and post-marketing, that are used to assess drug safety and efficacy. The problem is that regulators put about 70% of their effort into the pre-marketing evaluations, because that is considered "scientific". I believe that they need to do much more post-marketing surveillance, to establish how useful drugs are in real life conditions – but because so much of the existing evidence is considered unscientific and "anecdotal", this aspect of drug regulation tends to be ignored.

My next slides underline the reality, that the quality of most clinical trials is poor, and their evidence unreliable. This is what Marcia Angell, the editor of the New England Journal of Medicine, had to say about clinical trials, and she is not alone in this. I have some delicious quotes from *The Lancet* and the editor of the *British Medical Journal* saying exactly the same thing. (See slides). The leading medical journals all report the same problem: about 90% of the clinical trials that they receive cannot be published because they are not scientifically credible. They are statistically unacceptable, or the methodology is unacceptable, or the wrong inferences are drawn, or the results, as interpreted, are not justified by the evidence. Now, if that is what the editors of the leading medical journals are saying, you can be pretty sure that the standard with other medical journals is going to be no better than that. With many journals, it's probably going to be a lot worse. It's the same bell curve, isn't it? The best clinical trials are wonderful and indispensable, the worst ones are terrible and unpublishable, and the vast majority are probably not telling us anything much at all.

Before I talk about drug dosage, again to illustrate the limitations of clinical trials, I do want to underline that point about the significance of the bell curve. And I perhaps I need to do so to help put in context all the things I've been talking about. Because I have I have been making one criticism after another, I need to emphasise that there is a great deal more to be said about medicine than that. My abiding interest in medicine is

overwhelmingly to do with my admiration for what it stands for. Medicine is wonderful. At the top end of the bell curve, medicine is just spectacular, amazing. I mean, imagine understanding the human genome, it's a complete miracle. Medicine, at its best – both clinical medicine and research - is superb, and that is not in dispute. I love it, I admire it; it's the gold standard for me. But there is so much of it that is not "the best" – and when it *could* be so much better that is a real disappointment to be sure.

The underlying problem in pharmaceutical medicine seems to me to be to do with the failure to learn from mistakes. Consider the evidence. I was already an adult in 1960, at the time of the thalidomide crisis - when we first understood that the foetus was not immune to ill effects from drugs that the mother had taken. Then in about 1980, we discovered that there were different susceptibilities with older people, that older people needed, in general, lower doses of drugs. Again, this understanding arose because of a serious drug problem – the drug in question was an aspirin-like pain reliever recommended for osteoarthritis, benoxaprofen, and the problem emerged because the drug had barely been tested in elderly people – the very population who would use it most. Then around 2000, we discover that SSRI antidepressants like Seroxat aren't effective in treating children and can also precipitate suicidal behaviour. What's next? My guess would be that it will be to do with understanding the consequences of genetic diversity between individuals and how it affects drug metabolism, drug response and clinical outcomes. That is only a guess and not a very clever one at that, because we already know that there are significant differences, but we have yet to investigate just how significant they are going to be.

In the meantime, what do we do? In general, we act as if there is no problem, until the evidence becomes overwhelming – a tendency that is well illustrated by our approach to drug dosing. We recommend SSRI antidepressants, for example, on the basis that there is one single recommended dose, and that this dose is the one that everybody needs. It's complete nonsense. With the manufacturer's own data, you could say for certain that about half of all users of fluoxetine (Prozac) get about 4-times the dosage they need. The manufacturers have established that 52% respond to a 5-mg dose, but they only a make a tablet, or a capsule that can't be broken, that is 20-mg strong. So, what we are pretending,

and this is overwhelmingly for marketing reasons, is that ‘one size fits all’ - when we ought to be thinking about is about the subtlety of individual response.

This approach leads me to wonder if pharmaceutical medicine is on a collision course with itself. As medical science develops, we learn more and more about the subtleties of individual response - but as pharmaceutical companies develop and grow, they need to serve mass markets more and more. That explains the emphasis on ‘one-size-fits-all’ dosage recommendations. It’s for marketing reasons and because it’s a good way to sell drugs - because then the doctor doesn’t need to remember the dose. He/she just says to the patient, “Take one pill a day.” That is an important reason why today we have problems with drugs like Prozac and Seroxat – but what will the problem be tomorrow? In a way, that doesn’t terribly matter. The main thing that matters is that it will happen, unless we do something about it. My point is that we should take action, to prevent it. Instead of allowing history to repeat itself, we could and should so something about this system, which allows these mistakes to happen, over and over again.

In the next slide, I draw attention to one of the things we need to sort out, to help medicine to develop as more of a democratic enterprise. In this example here, I contrast what the scientist understands by “useful” knowledge, and what the ordinary person thinks is “useful” knowledge. If the risk of something bad happening to me is more likely than not, (>51% probability), I really want to know about it, and to take action to reduce or prevent that risk. But under the present system, the regulators really would quite like me not to know: they don’t want me to worry; they want me to trust my doctor and they want me to have confidence in them. The result is that I don’t get warned until there is near certainty (> 95% probability) of the risk. We’re back the “conspiracy of goodwill”, aren’t we? Our optimism allows us to speculate endlessly and extravagantly about drug benefits – but we hardly recognise the risks, in the absence of clear evidence of harm. Companies and regulators alike seem to need to count the bodies before they can ‘scientifically’ warn of risk.

**Underlying problems**

I want to touch very quickly on a number of other points, as I draw towards some conclusion. I could spend hours discussing any one of them, but perhaps some of them will come up later in your questions. Forgive me if I go too fast.

First, I want to emphasise that most new drugs are no better than older ones. That is true of anti-depressants, and it's true of most other drugs too. In the most optimistic estimates, about one new drug in every four offers some real advance over what is already available. And this leads to a key question: do we really want to put so much emphasis in drug policy on creating new drugs? Or do we need to think more about how we can use existing tools better than we use them now?

These questions bring us to an underlying problem that is becoming more and more relevant with the drive to globalization – it is to do with some deep conflict between trade and health imperatives. The drug companies need to develop new drugs and they need people to believe, as a generality, that new drugs are better than old drugs, in order to survive commercially. Again, this reflects something of the "conspiracy of goodwill". Anybody who is unwell, or who knows somebody who is unwell, yearns for new drugs – and I think there are something like 18,000 diseases that remain to be treated effectively, so it is self-evident that we need to invest in developing new drugs. But the question I'm asking is, do we need them so badly that we should emphasise drug innovation above all – and a further question is whether we should trust the major pharmaceutical companies, and market forces, to lead this vital social endeavour?

If only one new drug in every four offers some real gain, the cost of introducing one useful new drug - and I emphasize, 'useful' - might be about $4 - $5 billions. That's using the pharmaceutical company's own estimate. But does this make sense, when the total value of the African drug market in the year 2000 was 5.3 billion dollars? If the cost of developing each useful new drug, is about what is spent on drug treatments in the whole of Africa, it underlines a second proposition – that the need for new drugs must be related to targeting them at the areas of maximal medical need.

If there is any one subject on this list that I could speak about for hours and hours, it is this question of secrecy. But I don't want to get involved in it now, beyond saying that the secrecy there is in medicine makes the Department of Defence seem wonderfully

transparent. For all the evidence and data that is available, and I know it's overwhelming, the real evidence is hidden. When I say the 'real' evidence, I refer to the evidence that will allow us to make intelligent, informed decisions about benefit, risk and harm. When drugs are described as 'effective', based on the results of one or two trials in every eight, there is clearly an awful lot more we need to know. Much of the secrecy is unjustified and would be completely impermissible in almost any other industry or walk of life you could think of.

In the next slide, I continue this list of major underlying problems, but I only want to mention one of these things here. That is to try and explain the underlying dynamic that I believe is producing or intensifying the problems I've been describing. Developing useful new drugs is, of course, incredibly difficult. The research scientists who work on this do their very best and still they find it very difficult. That is completely understandable. The fact is the cost of developing new drugs has been rising very sharply, and the number of new drugs that is being produced now is no greater than it was a decade ago, although the expenditure is three times as high. In other words, productivity in innovation is going down.

This really is a threat to the major pharmaceutical companies, and they have responded in two ways. One is through the mergers and acquisitions that all of you will be familiar with. Seroxat was produced by SmithKlineBeecham, a couple of years later, SmithKlineBeecham became GlaxoSmithKline, and perhaps tomorrow it will be GlaxoSmithMerck. Company names come and go, and companies get bigger and bigger all the time. What the companies are trying to do by merging, and through acquisition, is to compensate for the lack of organic growth that this lack of productivity in innovation is causing. However, mergers are not solving the underlying problem they are only disguising it, and perhaps making it worse. The absolute size of companies – and the biggest are now huge – produces crippling overhead costs, and there is little or no evidence that greater size improves the productivity in innovation.

There is another consequence of this crisis in innovation; expenditure on marketing has hugely increased, particularly over the last 10 years. The problems here go further than the damage done by exaggerating drug benefits and playing down evidence

of their risks and harm. Because companies can't develop enough useful new drugs, they are turning their attention to developing new markets, and that means investing more and more in selling drugs, and suggesting more and more indications for them. Slowly but surely, drugs are now becoming an almost unavoidable part of everyday life. And as populations get older, you are going to see the consequences of this become more and more serious, if only because medical bills will become less and less affordable.

Yes we do need more drugs, but I am no longer confident that the major corporations, the leaders of the pharmaceutical industry globally, are the kinds of organizations in which we should be investing. In this slide, I use the term "institutional obesity", and it is not very polite, but I think it is fairly accurate. The major pharmaceutical companies today are too fat to be healthy, either for their own good or for society. I think in a way they know that, because the pattern of innovation is changing.

The major companies are now increasingly buying in research on new drugs, typically from much smaller companies; or they're buying ready-made drugs for tens or just a few hundred million, not the 800 million that it costs them to develop each useful new drug in-house. In this way, the pharmaceutical industry is changing: the major companies now seem to be developing into marketing organizations and large investment corporations, or banks, if you like. That is another reason why the way in which we control companies and relate to them should no longer be based on the premise that they are scientific organizations, protecting intellectual know-how. Their impact on society and our need for useful new drugs, and for the effective use of drugs, is just too important to allow this to go on to happen.

In this connection, I will also briefly mention one, I think, rather nasty and very unhealthy, feature of the new promotion – that is, the direct-to-consumer promotion of prescription medicines. In America, about $3 billion/year is now spent on promoting brand name prescription drugs to consumers. If you visit America, you will see television commercials day and night for prescription drugs: patients can't then go out and buy them, but they can go and nag their doctors for them, and there is strong evidence that they do.

I have two main concerns about direct-to-consumer advertising and this intensity of drug promotion. One is to do with the preservation of community and national health

services. For all its faults, the UK National Health Service is one of the main reasons that I feel very proud to be British. I think the National Health Service is pretty wonderful, and the idea of a National Health Service is absolutely wonderful. But direct-to-consumer advertising and the prospect of demand-led medicine make it impossible to imagine that any National Health Service would survive. It simply wouldn't be sustainable. I could show you the economics on the back of an envelope afterwards, but believe me, direct-to-consumer advertising, distinctly a product of the United States, would not be a good model to adopt in any country that invests in community health, as my country does. It is worth mentioning here that, in America, there are 40 million citizens who have no health insurance cover at all, and another 40 million who would be at risk of bankruptcy if the family was struck by a serious illness. Among the poorest are 2.5% of Americans who have health conditions that the World Health Organization says is comparable to that of a very poor developing country.

The lesson here from the US brings us back to the image of the bell curve: the best of American medicine is superb, but too much of it is not. There is certainly no evidence from the US that more drugs = more health. America actually doesn't look like a notably healthy society. How many Americans do you think satisfy all of these four requirements – that they don't smoke, eat a nutritious diet, are not overweight, and take good exercise? I wonder what you think the percentage is. The US government's Centers for Disease Control estimate the total number at around 3%.

We have so much to learn from the history of medicine. One of my heroes, Dr. Lewis Thomas, was once asked this question, in a seminar: "Why don't they teach the history of medicine in medical schools?" He replied: "It would be far too embarrassing to teach." But there is so much to learn from the history of medicine, and perhaps one of the most important lessons is that even the greatest experts are not always right. To my mind, the wisest doctor, the wisest professional of any description, is the person who understands how much they do not know.

My last two slides are meant to underline that we need to find better balance, and that the key to this is greater transparency – sunshine, to illuminate how much we know and how much more we need to understand. These are some of the issues my colleague, Professor Anita Hardon, and I have discussed in our book, *Medicines out of Control?* and

I very much hope that some of you will be able to read it. If so, you will understand that, in this talk, I have necessarily focused on the headlines – often without some important qualifications. But at least I hope that I have not left you with the impression that I underestimate the complexities of informed drug prescribing. I earnestly hope that you don't think, having sat and listened to me for so long, that I believe informed prescribing is easy. I don't. It means asking lots of questions, working very hard, thinking very hard, and being enormously understanding.

Part of that understanding means listening to patients: it can sometimes feel like looking for needles in haystacks - but think of the achievement when you do. We have an expression in England, "Trust me, I'm a doctor." I heard a patient the other day describing a conversation she'd had with a doctor - a bit of an argument really - and she ended it by saying, "Trust me, I'm a patient." It's not a bad idea.

I should like to thank the interpreters who worked so hard this afternoon: If you have understood what I've been talking about, and it feels to me as if you have, it is overwhelmingly due to the quality of their work. I'd like you all to look up there and wave in thanks to them.

Above all, I very much want to convey thanks to my most generous hosts, friends and colleagues. I am especially grateful to the Japanese Institute of Pharmacovigilance and to MedWatcher Japan for inviting me to talk and for the wonderful hospitality I have received in Japan..

And, finally, thank you all for your patience and understanding.