

**Overprescribing of Benzodiazepines: Problems and Resolutions**  
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**[SLIDE 1] Title slide**

Thank you for that kind introduction and for asking me to speak at this 3<sup>rd</sup> Annual Conference. I am honoured to be associated with this group, one of the few in the world which is seriously addressing an important problem with benzodiazepines – a problem which also applies to other prescribed drugs.

But actually it is a tragedy that there is a need for projects such as this. Why, more than 50 years after the introduction of benzodiazepines should we need organisations to disentangle problems which could and should have been foreseen?

**The birth of psychopharmacology**

It happens that I am old enough to have witnessed the start of the Era of Psychopharmacology – of drugs that affect the mind. Around the 1950s a whole host of such psychotropic drugs –all discovered by chance – entered the medical scene. These included the major tranquillisers such as chlorpromazine (Largactil), since developed into a range of antipsychotic drugs; it included the first antidepressants, the tricyclics and monoamine oxidase inhibitors, now joined by the SSRIs (selective serotonin reuptake inhibitors) such as Prozac; and it included the so-called minor tranquillisers, the benzodiazepines Valium and Ativan, now including a number of Z-drug hypnotics such as zopiclone (Sonata) and others.

These early discoveries were very exciting at the time, as they seemed to promise a cure for all psychiatric diseases. Schizophrenics taking antipsychotics could be let out of hospital to live in the community. Patients with depression could, allegedly, be freed from suicidal thoughts and from the perceived threat of electroconvulsive therapy (ECT). And the minor or major anxieties of life could be universally replaced with tranquillity and peaceful sleep induced by benzodiazepines. One eminent U.K. neurologist even wrote that from now on all mental illness could be cured by a handful of pills and there would be no need for psychiatrists.

At the same time it was believed, by a sort of backwards logic, that the causes of mental illness would be revealed by these drugs. Antipsychotics were found to block brain receptors for the neurotransmitter dopamine; therefore schizophrenia must be due to an excess of dopamine. Antidepressants were shown to increase the activity of the neurotransmitter serotonin; therefore depression must be due to a lack of serotonin. Benzodiazepines increased the activity of the neurotransmitter GABA, so anxiety must be due to lack of GABA.

Of course these naïve and simple hopes turned out to be in vain. 50 years later we still do not know the cause of schizophrenia or depression or even how the drugs work. The prognosis of these illnesses and of anxiety states has changed little. It has become clear that the drugs, including benzodiazepines, do not cure anything; they do, often usefully it must be said, control some symptoms but have little effect on the underlying

processes. And, as everyone here knows, the drugs carry their own disadvantages. But these same drugs have made millions for drug companies.

### **The influence of the pharmaceutical industry**

One activity that the new discoveries engendered was a neurotransmitter hunt. There was a search, mainly in the pharmaceutical industry, for new drugs acting on dopamine, serotonin or GABA. Once the basic work had been done, drug companies did not have to foot the cost of developing new drugs. It was much cheaper to manufacture “me too” drugs with similar actions but perhaps fewer side-effects. As a result, the world ended up with over 20 different but similar compounds in each class of antipsychotics, antidepressants and benzodiazepine and other sedative/hypnotics. “You have to go where the market is”, remarked one scientist working for a drug company.

And there was a change in the way drug companies were run. This is a quote from Pierre Simon, a pharmacologist working for Sanofi Pharmaceuticals, taken from David Healy’s book *The Pharmacologists*: “In the beginning, the pharmaceutical industry was run by chemists ... This was not so bad. [But] now most of them are run by people with MBAs, or things like that, people who could be the chief executive of Renault, Volvo or anything. They don’t know anything about drugs.” But, clearly, they do know where the market is.

Another quote from the same pharmacologist: “When you find a drug that is really active on one receptor .... The problem comes when you present it to the financial analyst. You say ‘I have a new drug, a very interesting antagonist of [receptor X]’ ‘Good’, says the financial analyst, ‘what is the market?...’ So you have to decide for what indication the drug should be developed at what dosage, what will be the price of the drug, and so on.” So the pharmacologist has to decide for what indication the drug will be developed. If the indication is not there, it must be created – in other words a disease suitable for the drug must be invented.

One of the many examples of this process was the development in the 1970s of Xanax (alprazolam), a very potent benzodiazepine, for panic disorder. According to Dr. David Sheehan at the Institute of Research and Psychiatry in Tampa, Florida, the marketing of this drug involved “a clear strategy” to take advantage of the medical profession’s current confusion about the classification of anxiety disorders and (I quote:) “to create a perception that the drug had special and unique properties that would help it capture a market share of benzodiazepines and would displace diazepam from the top position.... There was in fact nothing unique in this regard about Xanax .... All the benzodiazepines were good for panic disorder.” Xanax was marketed by Upjohn with approval of the FDA (US Food & Drug Administration) in doses of up to 6mg (equivalent to 120mg of Valium).

Some vignettes provided by Dr. Sheehan give an insight into the rather cavalier way in which trials with alprazolam were conducted. There was no suitable animal model of panic disorder so it was decided to try it out on a small group of patients who had panic attacks. “It was dark; it was fall in Boston” said Dr. Sheehan. “I particularly remember two sisters who were so phobic of medication, that they asked if they might take the medication in the unit so that I could rescue them if anything bad happened... So they took two alprazolam tablets in the waiting room, waited for 30 minutes and then felt ok and decided to take the subway home. I was still in my office when I got a phone call. It was

the two sisters; one of them had got a phenomenal effect, was sedated and ataxic and had to be helped off the train and got home by her sister. They called me up and one sister said 'This is incredible, she's cured'.

"Another patient in this group, a dynamic executive type, phoned the next day and said 'Doc, I am lying here on the couch in my office'. "Oh my god, that's terrible", I replied. 'No Doc this is not terrible at all', he said, 'I haven't felt this good in 10 years, you have no idea what a relief this is. I feel so calm, I just don't feel any anxiety, it's really wonderful'.

"Then a further group of these patients in the study said 'Doc, this is amazing – there are so many panic patients out there in the world... the company that makes this is going to make a fortune ... You should buy stock in this company – you won't have another opportunity like this.'"

History does not relate what happened to these patients if they continued to take Xanax long-term. But there is no doubt that Upjohn had a field day. Xanax duly overtook Valium as the most widely prescribed benzodiazepine. Xanax was dropped from the U.K. limited list in 1985, but it is still available on private prescription, and it is still widely prescribed in 4-6mg doses in the US and I get calls every week from people having long-term problems with this potent drug.

### **Reclassification of anxiety disorders**

Alongside the development of Xanax, the confused psychiatrists were working on a new classification of anxiety disorders. Panic disorder became a new separate anxiety state in the new Diagnostic and Statistical Manual (DSM III) published by the American Psychiatric Association and at present anxiety, under a later DSM IV, is still split into separate categories which include panic disorder, agoraphobia, social phobia, other specific phobias and generalised anxiety disorder or GAD. But of course people with generalised anxiety get panics and develop agoraphobia and people with panics have generalised anxiety and other phobias. The inference of the new classification was that these separate disorders respond to different drugs, but in fact they merge together and they all respond to the same drugs include all the benzodiazepines and also to all the antidepressants including the old ones and the SSRIs like Prozac. If they all respond to the same drugs and the symptoms are common to all types, they clearly cannot be separate entities.

But of course you don't have to have anxiety to be prescribed a benzodiazepine. They have been prescribed for sports injuries, muscle spasms, premenstrual tension, exam nerves, depression, general malaise and much else. Because they make some people feel good at first, like the ladies on Xanax, these prescriptions tend to be continued long-term. I am sure everyone here knows how the long-term patients themselves – not the doctors – discovered that if you take benzodiazepines long-term you become dependent on them or, in common parlance, addicted.

### **Recognition of benzodiazepine dependence**

How the dependence potential of the benzodiazepines was overlooked by doctors when it was clear that they could replace their predecessors such as the barbiturates and meprobamate is a matter for amazement and casts shame on the medical profession which

claims to be scientifically based. Cross tolerance between different drugs, for instance between barbiturates and alcohol, was well understood at the time and clearly implied that if one drug could replace another it must have common characteristics and usually a common mode of action. In fact barbiturates and alcohol, like benzodiazepines, act on GABA receptors. The similarity between benzodiazepines and barbiturates was ignored (despite a few warning voices, including my own, which went unheard) and doctors were urged to prescribe benzodiazepines instead of barbiturates. They complied with such zeal that benzodiazepines became for a time the most commonly prescribed drugs in the world. Incidentally, they were helped by Roche who attacked barbiturates in order to sell their first benzodiazepines Librium and Valium.

The backlash came, as I have mentioned, when the patients themselves (particularly a vociferous group in the U.K.) complained that the drugs were addictive, mainly because they got withdrawal symptoms if they tried to stop. Eventually, in the early 1980s controlled trials of such patients by Malcolm Lader, Peter Tyrer and others demonstrated beyond doubt that withdrawal symptoms from regular therapeutic doses of benzodiazepines were real and that they indicated physical dependence on the drugs. Eventually the medical profession accepted officially, on the grounds that they produced a withdrawal syndrome, that benzodiazepines were dependence-producing, i.e. addictive.

Not to be outdone, the drug companies later produced a series of drugs that were not chemically benzodiazepines but produced the same effects. These were the Z-drugs zopiclone, zolpidem, zaleplon and now newly introduced eszopiclone (Lunesta). They were marketed as sleeping pills but in fact have similar properties to benzodiazepines. They act on GABA receptors, cause dependence and, like benzodiazepines, cause a withdrawal syndrome if used long-term. I will say more about these tomorrow.

With declining popularity of the benzodiazepines came a renewed interest in antidepressant drugs which led eventually to the SSRIs (selective serotonin reuptake inhibitors) – that we have today. It started as a deliberate tactic to displace benzodiazepines. Drug companies sponsored large international symposia attended by 100s, sometimes 1000s, of physicians where speakers warned of the harm benzodiazepines were doing because of dependence and suggested that serotonergic drugs would work not only for depression but were also good anti-panic drugs and good in generalised anxiety, social phobia and even in post-traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD).

The first serotonergic drug was a flop, but then Prozac came on the scene and was an immense success. So successful was Prozac that five different drug companies vied to corner some of the market with me-too SSRIs that are cheaper to make. Dr. Sulser of Vanderbilt University noted that if a drug company could get just 20% of the Prozac market it could make 400-500 million dollars a year with very little investment in research and development. The outcome of this is that we now have 5 other SSRIs in addition to Prozac. According to David Healy, the effective incidence of depression, OCD, social phobia, and PTSD has increased a thousand-fold worldwide since 1980.

### **New definition of drug dependence**

But there is a sting in the tail of this story too. After a while it became apparent from patients' experiences that SSRIs, like benzodiazepines, produced a withdrawal syndrome when they were stopped – in fact the withdrawal reaction is quite similar to benzodiazepine withdrawal. This is another example of surprising ignorance and lack of thought on the part of physicians. It was known that the older antidepressants, tricyclics and MAOIs (which were also beneficial for both depression and anxiety disorders) produced a withdrawal reaction – this had been well described by Peter Tyrer as long ago as 1984. Yet many doctors appeared to be taken by surprise by SSRI withdrawal reactions. Furthermore, doctors were not good at managing either benzodiazepine or SSRI withdrawal, a subject I will refer to in tomorrow's session.

As I mentioned before, the benzodiazepines had been accepted as being dependence-producing, or addictive, on the basis of their withdrawal effects. Now there were clear withdrawal effects from SSRIs. In a scramble to prove that SSRIs were not addictive, psychiatrists changed the definition of drug dependence. Criteria for substance dependence were altered in the 1994 DSM IV by the American Psychiatric Association.

### **[SLIDE 2] DSM IV definition of drug dependence**

In this edition, withdrawal effects alone were not enough. A patient now also had to have evidence of tolerance, drug escalation, continued use despite efforts to stop and other characteristics to qualify for dependence. And the withdrawal syndrome was replaced by the patronising euphemism “discontinuation reaction”. As if a patient would think there was some subtle difference between “discontinuation” and “withdrawal”. Actually, the benzodiazepines fulfil all these criteria for dependence.

### **International attempts to stem the tide**

So where are we now, 50 years into the Era of Psychopharmacology?” With regard to benzodiazepines, there have been attempts to stem the tide.

#### **United Kingdom [SLIDE 3]**

1988 – Committee on Safety of Medicines – bulletin to all doctors *Benzodiazepines are indicated for the short-term relief (2-4 weeks only) of anxiety or insomnia that is severe, disabling or subjecting the individual to unacceptable distress.*

*Benzodiazepines can cause or exacerbate depression and increase the risk of suicide.*

1999 – U.K. Department of Health – *repeated same message.*

2004 – Chief Medical Officer, Department of Health – *same message.*

#### **Canada [SLIDE 4]**

1982 – Health Canada

*Continuous use of benzodiazepines should not exceed 2 weeks.*

#### **New Zealand – [SLIDE 5]**

1989 – Department of Health

*Short-term treatment with benzodiazepines may be beneficial but use for more than 4 weeks could well be harmful.*

#### **Denmark – [SLIDE 6]**

2003 – National Board of Health

*Prescription of benzodiazepines should be restricted to a maximum of 2 weeks (sleeping pills) or 4 weeks (anxiolytics).*

## **Ireland – [SLIDE 7]**

**2002 – Report of the Benzodiazepine Committee**

*Benzodiazepines should not be prescribed for more than 1 month for anxiety or more than 2-4 weeks for insomnia.*

These are just a few examples of many world-wide efforts to reduce benzodiazepine prescribing. They have had remarkably little effect. I get e-mails, letters and phone calls almost every day from people all over North America, Europe and elsewhere who have been taking prescribed benzodiazepines for years and have run into problems with long-term effects and withdrawal (I will mention more about these in tomorrow's session). Benzodiazepines are still universally prescribed long-term, in excessive dosage with little regard to equivalent potencies (which I will also mention tomorrow) and often inappropriately to people of all ages.

## **Benzodiazepine Abuse**

One unfortunate consequence of this overprescription is a spillover of benzodiazepines into the drug scene. Benzodiazepines are now commonly taken by abusers of illicit drugs and sometimes used as recreational drugs on their own, and sometimes taken by injection, carrying all the same risks as other injected illicit drugs including hepatitis, HIV and AIDS. For anyone who doubts the addictive potential of benzodiazepines, this slide is an illustration [**SLIDE 8**] – eye, temazepam (Restoril) + explanation.

## **General measures to reduce overprescribing**

In conclusion, what can we do to improve the present situation? I have time to mention only a few measures.

First, I think the medical profession needs to rethink its attitudes towards psychotropic drug prescribing in general. The mentality persists that there is a pill for every ill; that every life problem requires medical treatment. This attitude was kick-started by the advent of benzodiazepines, naively thought at the time to be safe and non-addictive and so benign that they could with impunity be added to every household's drinking water, thereby improving everyone's quality of life. We need instead to turn our attention beyond the idea of drugs as cures for mental disease and look more at promoting basic and creative research towards causes and prevention.

At the same time, we should perhaps train more clinical psychologists to vigorously test and improve non-drug or psychological therapies, particularly for anxiety disorders and depression.

Secondly, we should somehow separate the pharmaceutical industry from health care policies. The interests of health and those of drug companies are not the same, and at present money, not science, is driving pharmacology. A U.K. government health committee heard evidence this year that industry-sponsored clinical drug trials are specifically designed to show new drugs in the best light, that negative trial results and adverse drug reactions are suppressed (as recently shown with heart disease associated with the anti-inflammatory drugs Vioxx and Celebrex, and suicides associated with SSRIs, and also long ago with epileptic fits caused by benzodiazepine withdrawal), and that selective

publication strategies, ghost writing of articles and financial sponsoring of doctors for meetings are widespread practices.

Yet of course we rely on drug companies as the only ones with enough funds to carry out large drug trials, and we must acknowledge the benefits they have bestowed on medicine with the discovery of new and often life-saving drugs. So we must devise policies that mutually benefit both the industry and the public health. I don't know what the situation is in the U.S. but one suggestion in the U.K. is to move drug company sponsorship to the Department of Trade and Industry (at present it is under the Department of Health, including the licensing of new drugs under the MHRA – Medicines and Health Care Products Regulatory Agency) and to preserve the Health Department solely for public health matters.

Thirdly, we should keep up the pressure on governments and health authorities to publicise what we see and hear every day – as indeed we are doing at this conference. We should continue to educate doctors, pharmacists, nurses, health practitioners of all kinds as well as the public to stick to the international guidelines for short-term only use of benzodiazepines. We should also campaign for better facilities such as support groups and withdrawal clinics for the thousands of people already damaged by thoughtless and profligate prescribing of benzodiazepines.

We have been slow to confront these issues and too few have taken up the cause. But, in the often quoted words of the anthropologist Margaret Mead: "... a small group of thoughtful citizens can change the world. Indeed, it is the only thing that ever has". So we must keep on trying.