ANTIDEPRESSANTS &
THE POLITICS OF HEALTHCARE

Jim Dobbins MP

I am the chair of the all party parliamentary group on involuntary tranquilizer addiction. We've been working on this for some time and we're trying to raise awareness of this very serious problem. In particular we want the government to accept that they have a role to play and that people who suffer from this kind of addiction are not abusers of the system. They are victims of the system. That's how I see it.

We're very pleased today to have Professor David Healy who is a psychiatrist, psychopharmacologist, scientist and author. He's here to talk to us about his view of this problem. I understand he may be saying some tough things but he's saying them for the best of reasons. I think we need to accept that. Pharmageddon is his book, and I understand the substance of this talk will be from this book itself.

David Healy MD

It's a great privilege to be here and I'm very grateful to Jim for having asked me.

My job this afternoon is threefold. One is to keep you awake. That's why there's a few hard hitting things in there. They aren't meant to be hostile - they're just hard hitting in a keep you awake way. Because of room and time changes I've had to cut the bit that makes it clear I'm not Pharma-hostile.

The second thing is to open up the debate about not just antidepressants and the issues about getting hooked on them but generally how we bring drugs into health care and how the problems of the antidepressants and getting hooked on them is just representative of the kinds of problems that we have with all drugs.

The third thing was to leave the talk open ended to stimulate debate but we've lost an hour so I'm not sure that will be feasible. We may be able to move elsewhere to debate and I'm happy to stay around.

I have a conflict of interest statement. I'm involved in an adverse event reporting website called RxISK.org. You can ask me anything about that afterwards if you want.

Here is the basic thrust of the talk. The BMJ for the last year has run a campaign about access to clinical trials data and you will all I'm sure have seen this. Those who are in favour of access to clinical trial data say – if we just knew what the drugs really do and can tailor the right drug to the right person we would be able to make sure that treatments work. And if they work we'll be able to provide health care in an efficient way either on the NHS for free or else highly efficiently if you're in private health care.

If treatments work,

they could be made available for free,

they would enhance national productivity,

and encourage innovation

If drugs don't work - and we can't know if they work if we aren't able to get access to the data – then neither the NHS nor private health care are going to work properly either.

Now the House of Commons recently produced a Paper about clinical trials being a good thing. Here you see Recommendation 4 from this document. This looks to me as though it's written in GSK Central. My basic argument is if you go along with this - and this is the Recommendation from the Clinical Trials committee - you are essentially handing healthcare over to the pharmaceutical companies.

We are not in favour of placing anonymized individual patient-level data (IPD) in the public domain in an unrestricted manner…

specific individuals sd be provided with controlled access to IPD through carefully managed and secure "safe havens".

Access should be facilitated by an independent "gatekeeper" responsible for insuring that the data … makes a useful contribution to scientific understanding

Page 4

I hope in the course of this talk to explain this claim in more detail.

I have a blog – davidhealy.org - which picked this issue up over a year ago and here again on the April Fool's Day post this year. It said that what the House of Commons have just done is exactly what GSK are hoping that the clinical trials committee would do. A year ago I put on the record that if we get the kind of access to clinical trial data that GSK want people to have we're going to hand things over to industry.

PHARMA NEWS

GLAXO BUYS OPEN SCIENCE!

Patents 'Sharing'. Promises full access

GSK: OPEN SCIENCE

1. NO DIVING
2. NO FISHING
3. NO LOOKING

GSK OPEN SCIENCE: SAFE SECURE SECRET

We are not in favour of placing anonymized individual patient-level data (IPD) in the public domain in an unrestricted manner…

specific individuals sd be provided with controlled access to IPD through carefully managed and secure "safe havens".

Access should be facilitated by an independent "gatekeeper" responsible for insuring that the data … makes a useful contribution to scientific understanding

Why is this the case?

Well let me take you back to the 1960s. My parents were thinking at the time of buying a car. It was a time when people didn't need cars. My father could get to work easily on the bus or the train. The local shops were close to us so that you could walk to get all the bits and pieces that you needed.

My parents opted to buy a car. A car was a luxury. Fairly soon afterwards Ireland changed, Dublin changed, and most people began to need a car because they were living further out and work was too far away and the local shops weren't local in the way they had been before and the kinds of things you needed couldn't be got in the local shops the way they could be before.

We all got cars and because we had cars cities changed so that the city itself became a vehicle to sell cars. This is what the marketing departments of major companies would call a distribution channel - where everything conspires to sell the product. Cities, the way we lived, all meant we needed cars. Companies market types of cars – never the idea you might need one.

Cars can be an unquestionably good thing. If either Jim or I have a heart attack here this afternoon we will be thrilled that there's an ambulance out there able to take us to hospital quickly. But cars are also inextricably linked to a change in the world in which we live, to climate change, a change of the kind that most of us as individuals find hard to see how we could influence.

In much the same way during the 1960s, my parents wondered if we needed a TV. You didn't need to have a TV back then but it just looked like a good idea. Fairly soon afterwards as the news broke on TV it became inconceivable to most people that they wouldn't have a TV. And as TVs

hooked up with computers to create the informational super highway we have entered a world now where you absolutely have to be hooked up or you're not alive. There isn't really an option. Everything conspires to sell the product.

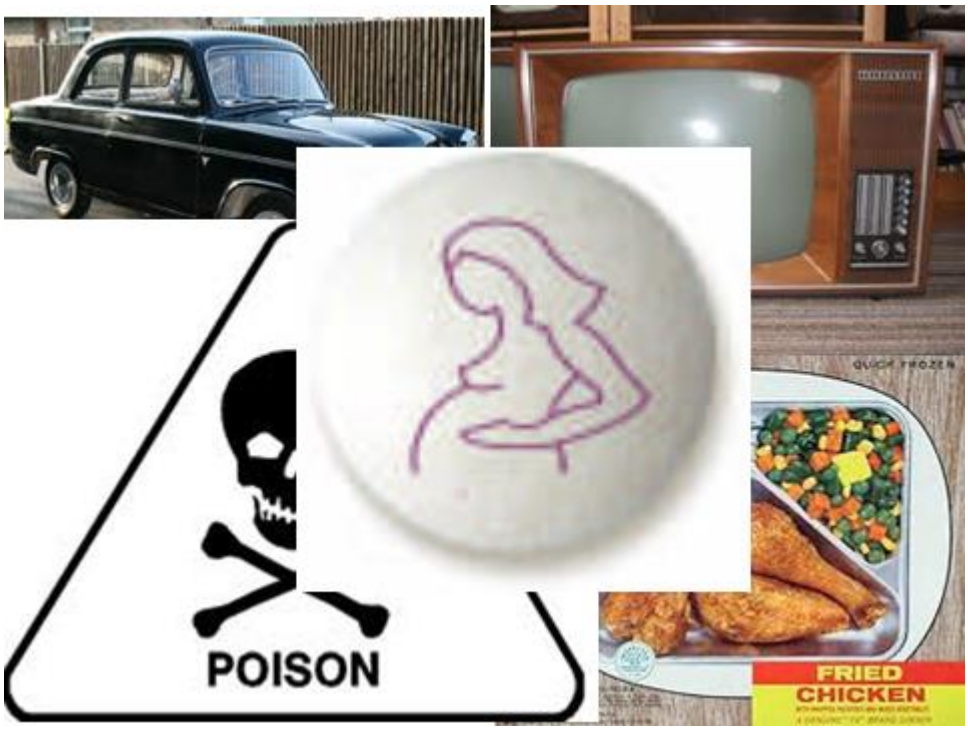
The informational super highway looked close to adverse effect free until *The Guardian* revealed there could be risks to all this that we weren't aware of beforehand. If you are not hooked up you might get a bunch of US SEALs turning up at your door one day and killing you because, well if you aren't hooked up to the superhighway, there must be something wrong with you.

Back in the 1960s it was rare for children to come home from school to a processed meal. There were no fast foods. But as the way we lived changed during the 1960s and as we didn't buy fresh food locally in the way we had before, instead using our cars to go to hypermarkets to buy food for the week, increasingly we began to buy processed foods.

Now unlike the informational superhighway and climate change it's clear to an awful lot of people - perhaps most of the people here in this room - that fast foods aren't the only way to go. They can be optional but they aren't the way we should eat routinely. There has been a slow food movement that has begun to counteract the fast food movement.

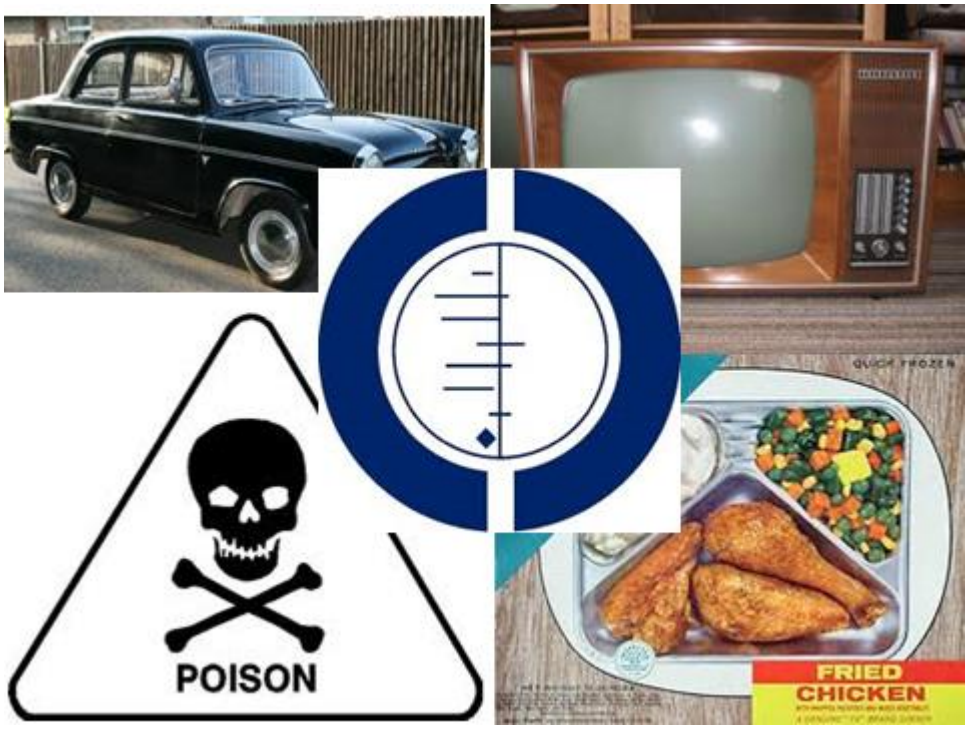
In just the same way as for food, cars and televisions, back in the 1960s drugs were not the only answer to health care problems. They were an option. They were a poison that it was great to have it and doctors could use with care. But we have moved into a world these days where as opposed to being regarded as poisons that could be tremendously useful if used wisely drugs – and this includes the antidepressants – have become something closer to fertilizers to be used indiscriminately.

The symbol that you see here is a proposed stamp to put on antidepressants to overcome the scruples women might have about taking antidepressants during pregnancy. There is a serious proposal to stamp drugs this way despite the evidence that points to the fact that antidepressants double the rate of birth defects, double the rate of miscarriages, increase rates of voluntary terminations and potentially lead to developmental delay in children born to mothers who have been on them during pregnancy. Yet we have proposals to try to encourage women to have these drugs during pregnancy.

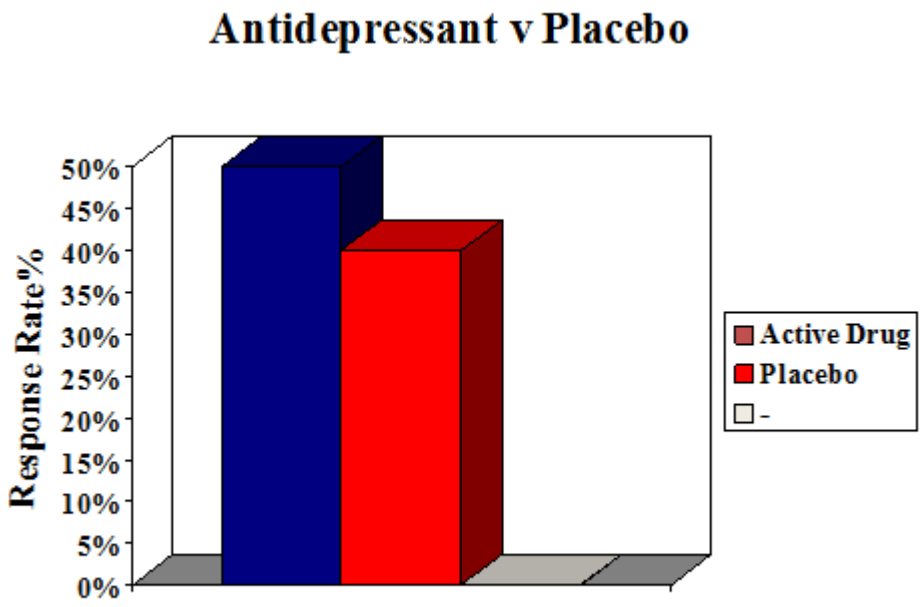


Just as cars come inextricably linked to oil, there's a further component linked to pills that has played a big part in this transformation of medicine. This will come as a big surprise to all of you - it's the controlled trial. This is the symbol here for the Cochrane Centre. Controlled trials linked to pills are driving a change in health care of the kind few of us want to see.

Let's see if I can make this point a little bit more clear.



Here in this slide is the data that the controlled trials for the antidepressants, data from 100,000 people. It shows that the antidepressants just about beat placebo in controlled trials. Even the experts divide on what this means. Some say that data like this showing that antidepressants just about beat placebo prove antidepressants work. Others say it shows that for the most part we should not be treating people with antidepressants.



Stone and Jones Nov 17th 2006: FDA

I want to take you into this in more depth This is not a high powered academic talk so at this point don't panic.

You have never seen a controlled trial of a parachute. If a treatment works we don't need controlled trials. But the world of evidence based medicine in which most of us live and get treated assumes that we do controlled trials on drugs to show that they work. There is a linguistic curiosity here. The word evidence in most European languages means something like taking the evidence of your own eyes at face value. Evidence based medicine in English means just the opposite - it's all about trying to persuade people to take things that naturally they may not be instinctively keen to do. It's about persuasion, and it undermines the evidence of your own eyes.

As a thought experiment we're going to bring one of these plants on the market as an antidepressant to show the problems controlled trials can cause. On the upper right you've got stimulants and there are loads of trials showing that the stimulants "are antidepressants". On the lower right you've got nicotine and again there are lots of trials showing that various cholinergic agents work well as antidepressants. On the lower left you've got opium which was used routinely during the 19th century to treat severely depressed people. There's no doubt that using the procedures that got Prozac on the market as an antidepressant, we could make opiates into antidepressants -– and in fact an opioid has just been fast tracked as a potential antidepressant by FDA. In the middle you've got Broccoli the only plant that contains benzodiazepines, and there are lots of trials showing benzos making it as antidepressants.

The reason these drugs aren't antidepressants is that for the most part companies can't take patents out on them as antidepressants.

But we're going to bring wine on the market as an antidepressant using the same procedures that gave us Prozac.

To do this we would have to run a controlled trail comparing a red wine with a red coloured water perhaps GSK's Ribena. We have to get two positive trials in people with "nerves" or stress who can be regarded as being depressed. The trials only have to last for six weeks.

The outcomes or evidence at the end of the trial that Wine works wouldn't be whether the people who were depressed got back to work or that we were able to show that alcohol saved lives compared to placebo alcohol. It's just an issue of showing a rating scale difference where some of the items of the rating scale are "is a person less anxious than they were before", "are they sleeping better over the last few weeks than they were beforehand". Comparing alcohol to Ribena on a rating scale like this would unquestionably produce a difference.

We only have to get a "positive effect" like this in 2 trials out of 10. Even though there are only 2 positive trials our company can generate up to 100 publications saying that alcohol works wonderfully well as an antidepressant. These will all be ghost written articles. On average companies produce 30 to 40 articles per clinical trial done giving you the impression that there have been lots of clinical trials done when in fact there may be extraordinarily few. We don't have to let the world know about the 8 trials that were done when alcohol was negative compared with placebo.

In the course of these trials if there are some shining examples of people who drank red wine, a glass or two each night, and at the end of the treatment trial said this was absolutely fabulous, the best six weeks of my life, our ghost

writers will be able to take those instances and write them up as representative instances of just what the effects of alcohol are. We wouldn't have to mention the fact that for most people placebo does just as well as alcohol.

Efficacy

1. 6 Week Trials
2. Rating Scales
3. 2 positive out of 10 trials
4. 100 publications
5. Accentuate the positive
6. All effect down to alcohol
7. Mexican alcohol

8. Gin, whiskey, beer, wine & rum
9. Scotch, Irish & Japanese whiskey

10. NICE Guideline endorsed
11. Cost-Utility Analyses ++
12. Take life long - NNTs

Now here's one more trick to help us get alcohol licensed. In a recent trial of a drug brought on the market as a mood stabiliser, the company did a trial in 30 US 2 Mexican hospitals. In the 30 US hospitals the drug did not beat placebo. In the two hospitals down in Mexico everybody that got the active drug did wonderfully well and all those who got placebo did poorly. When you added the Mexican hospitals to the 30 US hospitals overall the drug marginally beat placebo. FDA looked at the data, said it's interesting that there is such odd data from Mexico but we're not going to look into that - we're just going to approve this drug as a mood stabiliser.

We can do exactly the same thing with alcohol – perhaps using the Isle of Man. I defy anybody here in the room to say to me that under these conditions we couldn't get 2 trials where we can show that active alcohol beats placebo alcohol.

Now let's say the conditions were there for us to patent alcohol as an antidepressant and Jim and I brought whiskey on the market as an antidepressant - and in this case whiskey spelt with an 'e' because I'm Irish – the rest of you here in the room could bring gin onto the market as an antidepressant, or beer, or wine or rum. And patients would end up potentially being on combinations of gin and whiskey and beer and wine and rum because these have all been proven to be antidepressants. We could even get to the stage that you might be put on Scotch and Irish and Japanese Scotch.

You know for certain NICE would write guidelines to say that alcohol was the No. 1 antidepressant - that this is what most doctors in the country should be using first. Because NICE can only go on the published evidence. They don't have the data, they don't have the negative trials. They just have the data as written up by the ghost writers. And if our publication strategy is good we will be able to bring alcohol onto the market with a bunch of articles that make it compulsory for NICE to endorse alcohol as the antidepressant that should be used first.

We have economists as you know who will be able to prove that even if we pitched alcohol at an extremely expensive price it's going to save the NHS money if as many people are put on alcohol as can be because of course they will be able to perform much better at work when we've "cured" their underlying mood disorder.

And finally on the basis of these six week trials patients will be recommended to take alcohol for the rest of their lives.

As regards the adverse effects of alcohol remember these were only six to eight week trials and taking red wine at night for six to eight weeks isn't going to produce much in the line of adverse effects. In any articles they write, our ghostwriters may opt only to report the adverse effects that occur at a 10% rate or more. If there's any compelling clinical story about a person who has had a bad experience of alcohol we'll be able to disregard it as anecdotal – the Ian Hudson approach towards adverse events.

Side Effects

1. 6-8 week trials
2. 10% or more?
3. Anecdotes – Disregard
4. Pregnancy
5. Suicide & Violence
6. Dependence - illness
7. LFTs - depression

Prescription only Med

1. Amphetamines
2. Risk laundering
3. Stockholm syndrome
4. Legal liability

.

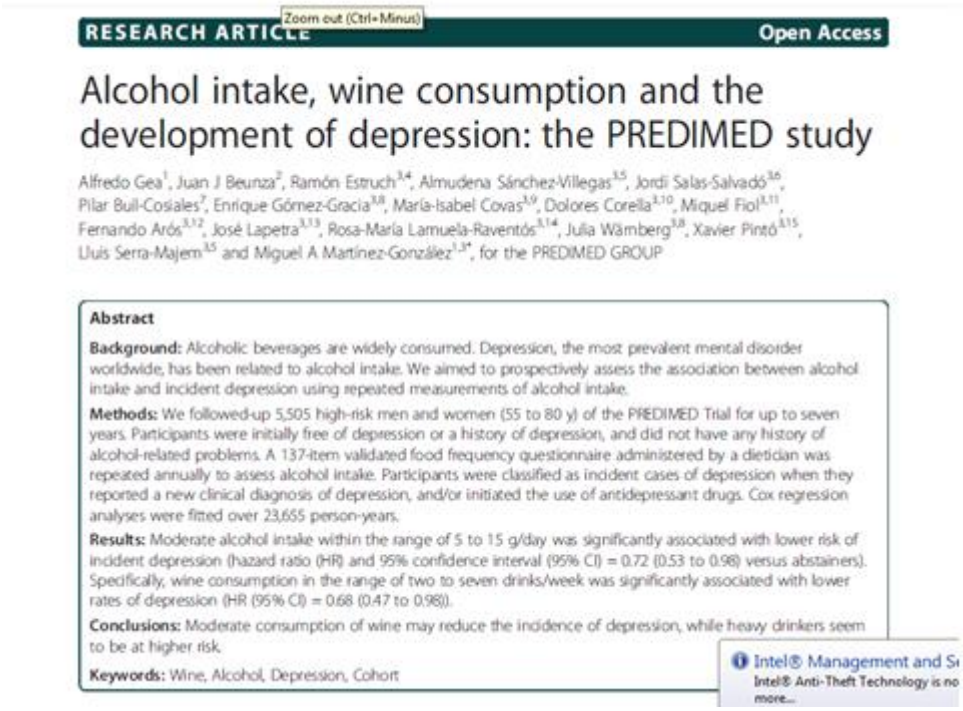
These days if you go out for a meal and you're pregnant and you've a glass of wine in your hand there's every chance it will be ripped out of your hand by

other people in the room. In fact it is much safer to drink a glass of wine every night of your pregnancy than it is to take an SSRI.

I'm sure few of you here in the room would think it conceivable that a glass of red wine per night would double the rate of suicidal acts in six to eight week trials. It's just not going to do it. But that's what the data shows SSRIs do

In terms of people stopping alcohol after they recover and feeling worse, if they say: "I seem to be feeling anxious, more nervous, could I have got hooked?", we know that doctors will say to them no, you've got an alcohol deficiency disorder, you need to stay on alcohol for the rest of your life. We can depend on doctors to do this.

Just in case you think this is all an engaging spoof, well look at this recent article that has just come out showing alcohol is quite a good antidepressant. If you're routinely taking red wine as part of a Mediterranean diet you are much less likely to get depressed than other people.



Zoom out (Ctrl+Minus)

RESEARCH ARTICLE Open Access

Alcohol intake, wine consumption and the development of depression: the PREDIMED study

Alfredo Gea[1], Juan J Beunza[2], Ramón Estruch[3,4], Almudena Sánchez-Villegas[3,5], Jordi Salas-Salvadó[3,6], Pilar Buil-Cosiales[7], Enrique Gómez-Gracia[3,8], María-Isabel Covas[3,9], Dolores Corella[3,10], Miquel Fiol[3,11], Fernando Arós[3,12], José Lapetra[3,13], Rosa-María Lamuela-Raventós[3,14], Julia Wärnberg[3,8], Xavier Pintó[3,15], Lluis Serra-Majem[3,5] and Miguel A Martínez-González[1,3*], for the PREDIMED GROUP

Abstract

Background: Alcoholic beverages are widely consumed. Depression, the most prevalent mental disorder worldwide, has been related to alcohol intake. We aimed to prospectively assess the association between alcohol intake and incident depression using repeated measurements of alcohol intake.

Methods: We followed-up 5,505 high-risk men and women (55 to 80 y) of the PREDIMED Trial for up to seven years. Participants were initially free of depression or a history of depression, and did not have any history of alcohol-related problems. A 137-item validated food frequency questionnaire administered by a dietician was repeated annually to assess alcohol intake. Participants were classified as incident cases of depression when they reported a new clinical diagnosis of depression, and/or initiated the use of antidepressant drugs. Cox regression analyses were fitted over 23,655 person-years.

Results: Moderate alcohol intake within the range of 5 to 15 g/day was significantly associated with lower risk of incident depression (hazard ratio (HR) and 95% confidence interval (95% CI) = 0.72 (0.53 to 0.98) versus abstainers). Specifically, wine consumption in the range of two to seven drinks/week was significantly associated with lower rates of depression (HR (95% CI) = 0.68 (0.47 to 0.98)).

Conclusions: Moderate consumption of wine may reduce the incidence of depression, while heavy drinkers seem to be at higher risk.

Keywords: Wine, Alcohol, Depression, Cohort

Intel® Management and Se
Intel® Anti-Theft Technology is no more...

Now if we were in fact to get wine licensed as an antidepressants all of you can see what a disaster this would be. You can see this because you know with the evidence of your eyes – not from controlled trials – what alcohol can do.

Well, the SSRIs and antidepressants are available on prescription only precisely because we have every reason to believe they will turn out to be more dangerous than wine but your doctors, the MHRA and the government are treating these drugs as though they are much safer than alcohol. It is close to national policy to get as many people as possible on antidepressants – and other drugs from statins through to hypoglycaemics.

The harm we are wreaking on individuals lives, and the public health in general, not to mention the morale of doctors or patients who refuse to go along with this is as great if not greater than if we were enforcing compulsory alcohol use on a mass scale.

The point I'm trying to get at is about controlled trials and what they show and don't show. I don't want you to get the idea that I'm saying all controlled trials are wrong. They aren't. Controlled trials can be extraordinarily helpful. But the best way to frame it probably is that All Trials do harm, some may also do good.

There are trials like the Women's Health Initiative trial which conclusively helped us locate the place of HRT in treatment. Where before it had been used widely, since then people have been much more cautious about its use afterwards.

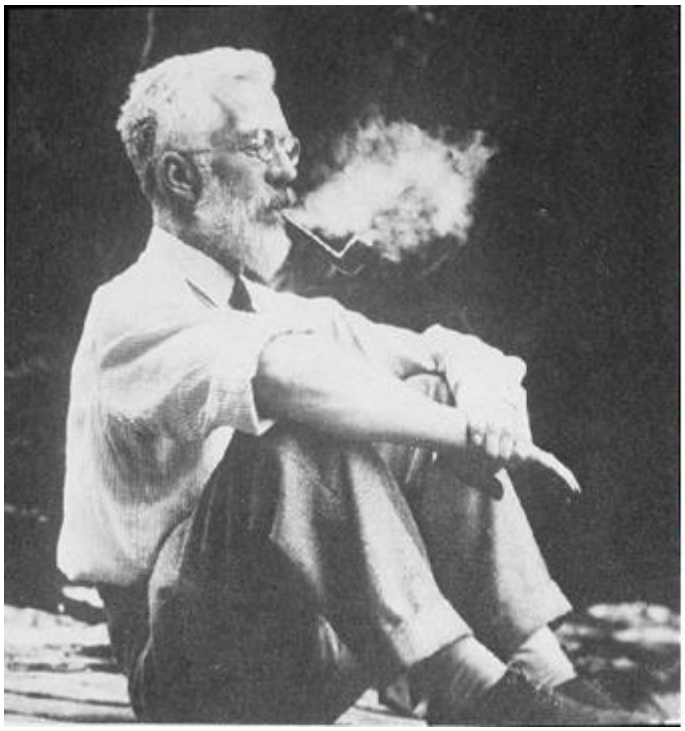
All RCTs do harm
Some may also benefit

If we ran the same kind of trials on the SSRIs, trials that lasted for months and years as opposed to six to eight weeks, trials that recruited tens of thousands of people, what would the conclusions about SSRIs have been faced with high rates of people getting hooked on these drugs, more lives lost to suicide than saved, a greater rate of birth defects?

Such a trial would have functioned in a completely different way from the way company trials do. But it's now government policy as a mark of quality to try to get as many people into SSRI type RCTs as possible.

Where are the problems coming from?

Well, controlled trials were invented here in the UK and it's a tricky thing to cast doubt on them here. The key person in their origin is Ronald Fisher. Fisher was responsible for the ideas of randomisation and statistical significance. Randomization was a way to control unknown unknowns by randomly assigning some people to treatment and others to placebo.



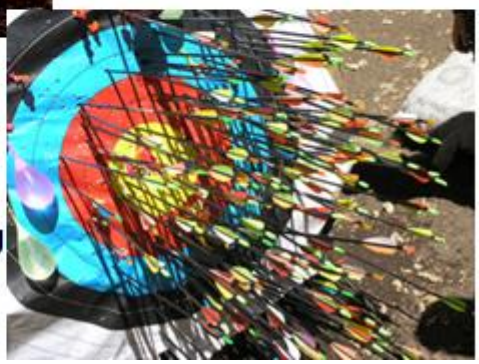
R.A Fisher, Design of Experiments. Edinburgh: 1935.

Randomization

Statistical Significance

But Fisher developed the idea of controlled trials in the context of proving that fertilizers worked, not medicines. For Fisher, the idea that a controlled trial showed a fertilizer was statistically significantly likely to work meant he had a William Tell type effect - that is if you ran the trial you got one result and every single time you ran the trial you would get the same result. That's what he meant by statistical significance.

But if you look at the trials for antidepressants or hypoglycaemics or antihypertensives or almost any drug you care to think of the data, in particular for the antidepressants, looks more like this. We're not getting the same result every single time, we're not doing with randomisation what Fisher designed it for and that's partly because it's not absolutely clear that randomised controlled trials work for medicines in the way they work for fertilizers.



Statistical Significance means
- **You know what you are doing**
- **You get the same result each time**

Part of the issue is that in the case of fertilizers you're just looking at one effect. You only want to see if there are more ears of corn. But of course when we give a drug to a person the chemicals that are called drugs don't just do one thing. They can do a hundred things and both the patient taking the chemical and the doctor giving the chemical may be as interested in the other 99 things as in the 1 thing that the pharmaceutical company is interested in.

FERTILIZERS	DRUGS
• 1 Effect	• *100 Effects*
• Hard Outcomes	• *Surrogates*
• Population Effect	• *Individual Patient*

Logically Ungrounded

Placebo Fertilizer?

Another thing is in the case of ears of corn you can count them but for the most part, as explained in the alcohol example, in the case of medicines we're not looking at a hard outcome such as whether there more people back in work or more people alive at the end of the trial. It would make little sense to anyone to use this kind of outcome to test if a fertilizer works.

Finally in the case of fertilizers you are looking at population effects. But medicine is critically concerned with the effects on the individual person.

Very few people know this but the philosophy of controlled trials isn't worked out. We are told that they're a gold standard but no-one knows what they actually do. And of course no one has ever seen a controlled trial of a placebo fertilizer.

This image tries to bring the point the difference between fertilizers and medicines. Farmers and agriculturalists are concerned with population effects doctors are concerned with the individual patient. If an individual ear of corn dies, that's no problem. If an individual child dies because of a drug that's a hell of a problem.

Now the person most responsible for controlled trials is a man called Louis Lasagna who was the Ben Goldacre of his day. In the 1950s and early 1960s Lasagna was the most famous doctor in the world. He's the person responsible for the placebo response, the person who did most to promote controlled trials, and the person responsible for informed consent and confidentiality.

He's on the right of this slide, a very charming and humorous man. His moment came when the thalidomide tragedy struck and we wanted an answer to the problems this drug caused.

Placebo Response
Controlled Trials
Informed Consent - Confidentiality

Louis Lasagna

In response, he introduced the idea that companies should be asked to prove not just that the drugs were safe but that they worked and this led to the 1962 FDA Act which is the same as the 1968 Medicines Act here which brought in the idea that companies had to prove their drugs worked through controlled trials.

operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess;".

EFFECTIVENESS AND SAFETY OF NEW DRUGS

SEC. 102. (a) (1) Section 201(p)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)(1)), defining the term "new drug", is amended by (A) inserting therein, immediately after the words "to evaluate the safety", the words "and effectiveness", and (B) inserting therein, immediately after the words "as safe", the words "and effective". 52 Stat. 1041.

(2) Section 201(p)(2) of such Act (21 U.S.C. 321(p)(2)) is amended by inserting therein, immediately after the word "safety", the words "and effectiveness".

(b) Section 505(b) of such Act (21 U.S.C. 355(b)) is amended by inserting therein, immediately after the words "is safe for use", the words "and whether such drug is effective in use". 52 Stat. 1052.

(c) Section 505(d) of such Act (21 U.S.C. 355(d)) is amended to read as follows:

Introducing trials to the regulatory apparatus made them what they have now become. Pretty soon after this happened, Lasagna began to have grave doubts about the wisdom of what the FDA had just done over in the States and what the Medicines Agency did here.

LOUIS LASAGNA

The days when a company would go to skilled doctors and give them a new drug and ask them to try it on some different patients seem gone. Is this cause for celebration or depression?

In contrast to my role in the 1950s which was trying to convince people to do controlled trials, now I find myself telling people that it's not the only way to truth.

In this slide you see his doubts - "Look, in the 1950s drug companies gave new drugs to doctors to see did they work and were they safe. We've changed to saying we bring drugs onto the market through controlled trials. Is this a good idea or not? Back in the 1950s I went around telling people they should be doing controlled trials. Now I'm going around the place saying for God's sake controlled trials are not the only answer".

Streptomycin – Because of RCTs

Antibiotics	Penicillins
Diuretics	Furosemide
Hypoglycemics	Metformin
Antihypertensives	Thiazides
Antihistamines	Diphenhydramine, Chlorphenamine
Antipsychotics	Clozapine, Haloperidol
Antidepressants	Imipramine
Minor Tranquilizers	Diazepam
Stimulants	Dexamphetamine, Ritalin
Steroids	Prednisone
Contraceptives	COC – The Pill
Chemotherapies	
Anticonvulsants	Valproate, Phenytoin
Analgesics	Morphine, NSAIDs
Vaccines	Polio, Smallpox

Now if you look on the left here, you've got all the drug groups introduced during the 1950s without controlled trials. The first antidepressants, antipsychotics, antibiotics, antihypertensives, hypoglycaemics were introduced without a controlled trial in sight. And in fact if you look at the representatives from these drug groups of the 1950s and compare them with the antihypertensives, antidepressants, antipsychotics or hypoglycemics we now have – almost universally the newer drugs, introduced through controlled trials, are weaker than the drugs introduced during the 1950s.

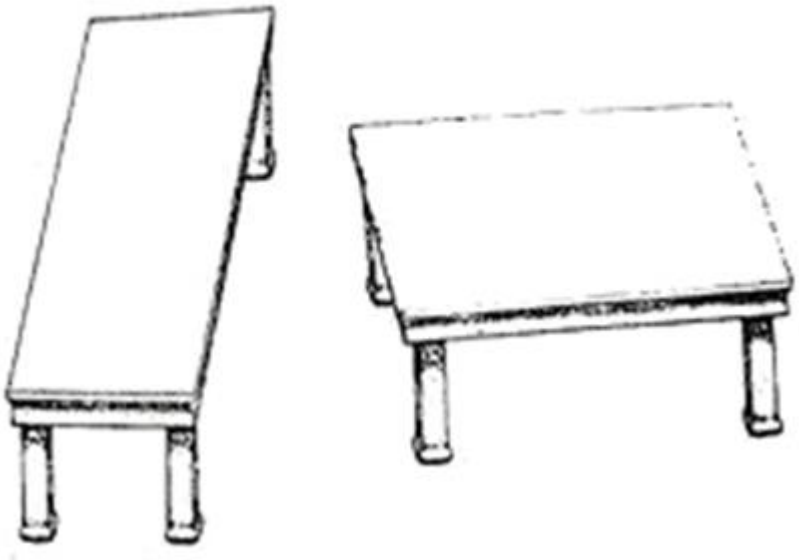
Why would this be? Well, in the 1950s when a company put a drug on the market it had to be obvious to the doctor using the drug when he gave the drug to you that it made a difference to you. He saw any differences for the better or the worse.

Nowadays in a controlled trial we might give all members of parliament either an active drug or placebo and nobody might spot a clear cut benefit but yet there can be a statistical benefit a marginal difference.

Let me introduce you to one more idea. If you're confused, do not adjust your set. If Michael Rawlins, Iain Chalmers, Ben Goldacre or any of the experts on controlled trials were here they wouldn't be able to explain this to you.

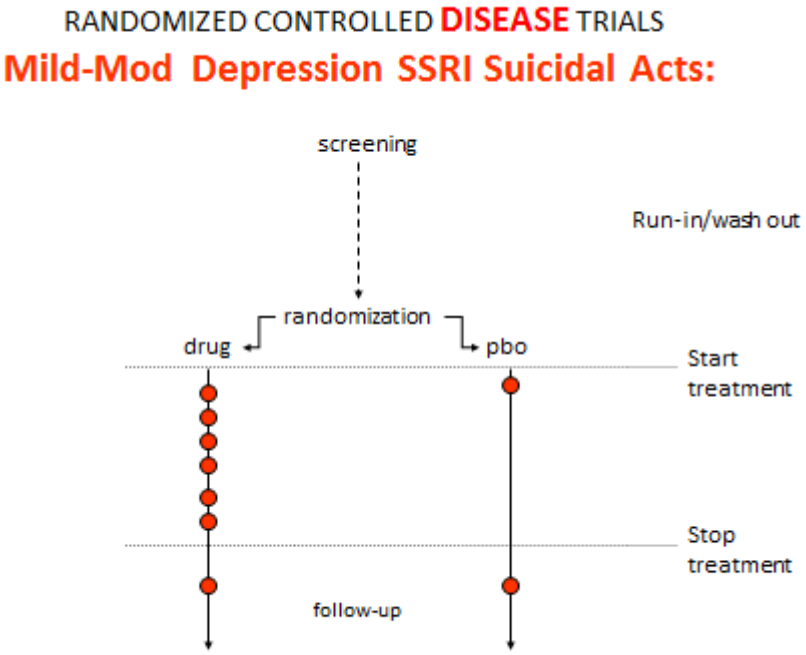
So this is confusing, but it points to deep-seated problems in controlled trials you don't usually hear about.

CONFOUNDING



The two tables there are exactly the same size and shape. They don't look like this to you but they are. And even if you were to trace one onto the other and prove to yourself that they are the same shape they would still look different.

Here's how this applies to controlled trials. This is what the data on suicidal acts on the SSRIs looked like. There's an increased rate of people who went on to a suicidal act compared to placebo. When it got to the point of being statistically significant MHRA and FDA said this shows that these drugs can cause people to become suicidal.



This is wrong. What the data shows is that overall there's an increased rate of people going on to a suicidal act. In mild to moderately depressed patients these drugs do not save lives.

But that's not the point I'm trying to get at. What I'm trying to get at is this. The SSRIs are a fairly weak group of drugs. Before the SSRIs were brought on the market we had the tricyclics which were a more potent group of antidepressants. In any trials done with the TCAs when compared with the SSRIs, the TCAs win hands down.

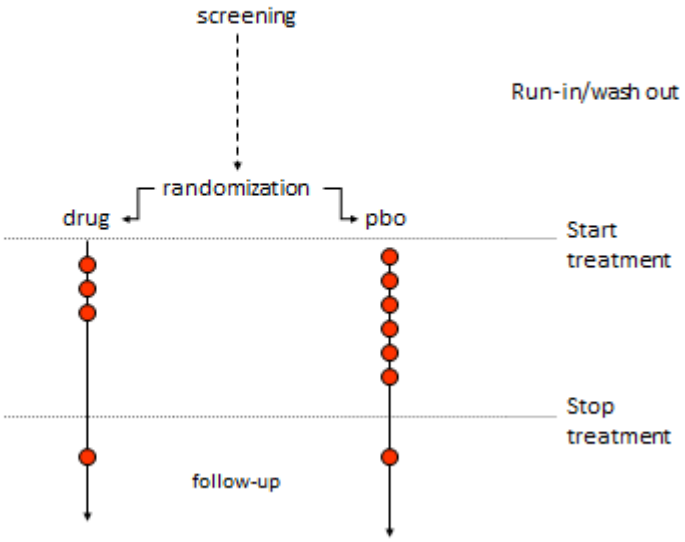
TCAs like imipramine treat melancholia, a severe mood disorder, in a way the SSRIs don't. Melancholics are at high risk of going on to commit suicide.

But TCAs like imipramine can also cause you to commit suicide. You can give these drugs to patients and see a patient become suicidal, stop the drug and the problem clears up, put them back on the drug and they become suicidal again.

There are clear reports of this from 1959. There is no question but that imipramine and amitriptyline can cause people to become suicidal but in a controlled trial of these drugs given to patients who have melancholia the data would look like this.

RANDOMIZED CONTROLLED **DISEASE** TRIALS

Severe Depression Imipramine Suicidal Acts:



A drug that can cause you to commit suicide can in a controlled trial done of severely depressed patients look like it is saving lives. The same drug put into a trial of mildly depressed people would produce a result that was exactly like the SSRIs – it would appear to lead to a net loss of life.

The result depends critically on an interaction between the drug and the disease. This is a problem that doesn't happen with fertilizers. This is a problem that randomization cannot overcome. When it comes to problems like this, if you go by the RCT evidence rather than the evidence of your own eyes far from being rational you are being ideological.

This isn't just true of the antidepressants. In the case of every drug, where the drug and the illness can produce superficially similar outcomes - the anti-arrhythmics, drugs for asthma, rosiglitazone for diabetes - controlled trials become unreliable. This is true for both adverse events as well as for the benefits of the drugs.

Here's yet another trick invented just a mile or two from here that should deepen your concerns about controlled trials. In 2006 GlaxoSmithKline were facing a serious problem. Their controlled trials had shown that in the case of people who had major depressive disorder there was a much higher rate of people going on to a suicidal act on paroxetine compared to placebo. This data was statistically significant. The company had a problem.

GlaxoSmithKline - 2006

Table 1. Summary of Events of Suicidal Behavior by Study Population, Treatment Group, and Age Band* (5)

Group	18-24 year olds			25-64 year olds		
	PAR	PBO	OR (95% CI)	PAR	PBO	OR (95% CI)
All Indications	17/776 (2.19%)	5/542 (0.92%)	2.4 (0.9, 7.3)	32/7543 (0.42%)	34/5000 (0.68%)	0.6 (0.4, 1.0)
Major Depressive Disorder†	3/230 (1.30%)	0/104 (0.00%)	Inf (0.3, Inf)	8/2713 (0.29%)	0/1567 (0.00%)	Inf (1.3, Inf)

Paroxetine Suicidal Acts 11 v 0 Placebo Suicidal Acts
N = 2943 N = 1671

So what they did was this. They added into the mix a group of patients whom they billed as having intermittent brief depressive disorder. In this group of patients again paroxetine is worse than placebo. There's an increased rate of patients going on to a suicidal act compared to placebo.

GlaxoSmithKline - 2006

Table 1. Summary of Events of Suicidal Behavior by Study Population, Treatment Group, and Age Band* (5)

Group	18-24 year olds			25-64 year olds		
	PAR	PBO	OR (95% CI)	PAR	PBO	OR (95% CI)
All Indications	17/776 (2.19%)	5/542 (0.92%)	2.4 (0.9, 7.3)	32/7543 (0.42%)	34/5000 (0.68%)	0.6 (0.4, 1.0)
Major Depressive Disorder†	3/230 (1.30%)	0/104 (0.00%)	Inf (0.3, Inf)	8/2713 (0.29%)	0/1567 (0.00%)	Inf (1.3, Inf)
Intermittent Brief Depression	10/35 (28.57%)	5/38 (13.61%)	2.6 (0.8, 9.4)	22/112 (19.64%)	30/113 (26.55%)	0.7 (0.4, 1.3)

Paroxetine Suicidal Acts 11 v 0 Placebo Suicidal Acts
N = 2943 N = 1671
RR > 6.0
Paroxetine Suicidal Acts 36 v 35 Placebo Suicidal Acts
N = 147 N = 147

Now watch - if you add the second group of patients to the first group as GSK did all of a sudden paroxetine saves you from becoming suicidal. This is a trick that any expert could have advised GSK to do.

GSK - 2006

Table 1. Summary of Events of Suicidal Behavior by Study Population, Treatment Group, and Age Band* (5)

Group	18-24 year olds			25-64 year olds		
	PAR	PBO	OR (95% CI)	PAR	PBO	OR (95% CI)
All Indications	17/776 (2.19%)	5/542 (0.92%)	2.4 (0.9, 7.3)	32/7543 (0.42%)	34/5000 (0.68%)	0.6 (0.4, 1.0)
Major Depressive Disorder†	3/230 (1.30%)	0/104 (0.00%)	Inf (0.3, Inf)	8/2713 (0.29%)	0/1567 (0.00%)	Inf (1.3, Inf)
Intermittent Brief Depression	10/35 (28.57%)	5/38 (13.61%)	2.6 (0.8, 9.4)	22/112 (19.64%)	30/113 (26.55%)	0.7 (0.4, 1.3)

Paroxetine Suicidal Acts 11 v 0 Placebo Suicidal Acts
N = 2943 N = 1671
RR > 6.0
Paroxetine Suicidal Acts 47 v 35 Placebo Suicidal Acts
N = 3090 N = 1818
RR < 0.80

Whenever we're uncertain about the nature of the illness we're treating, when there are reasons to think that there's a diverse group of patients in the treatment population, randomisation can act to hide the problem just as happens here.

So randomisation controls confounders when it comes to fertilizers but not some of the most important confounders when it comes to medicines.

Worse again by focussing attention on one outcome, it risks generating ignorance about ignorance for medicines. As opposed to controlling the unknown unknowns in a helpful way it makes us unaware of what we're unaware of because it gets doctors to focus in on 1 thing the drug is doing when there are 99 other things the drug is doing like causing people to get hooked to it that may be of much greater concern to doctors and patients.

But because the drug has been through a controlled trial, people get the impression that everything we need to know about this drug is known when in fact it is not.

To sum up, RCTs for the most part:

1. give weaker drugs,
2. produce standardised care – replacing medicine with mediculture,
3. lead to a world in which poisons are increasingly treated as fertilizers

(with older people in particular now likely to be on up to10 drugs chronically as opposed to just being on 1 drug briefly).

Here's Louis Lasagna again towards the end of his life quoting Bradford Hill the man who here in the UK ran the first controlled trial and outlining what Evidence Based Medicine does not and cannot do.

"If one came to the conclusion that the only way to find out the truth about a medication was to use a controlled clinical trial, it would mean not that the pendulum had swung too far but that it had come completely off its hook"

Louis Lasagna

Evidence Based Medicine has become synonymous with RCTs even though such trials invariably fail to tell the physician what he or she wants to know which is which drug is best for Mr Jones or Ms Smith – not what happens to a non-existent average person

So Lasagna because of the thalidomide crisis wrote controlled trials into the FDA Act but as of 1962 when the FDA Act came into being there had been only one placebo controlled trial on a drug done before that drug was brought to market. The mechanism that was put in place to stop thalidomide happening again had actually been employed by Louis Lasagna who had done a controlled trial for thalidomide showing it was effective and entirely safe. The mechanism put in place to stop thalidomide happening again was a mechanism through which this drug sailed without hindrance.

Reprinted from JOURNAL OF CHRONIC DISEASES, St. Louis
Vol. 11, No. 6, Pages 627-631, June, 1960 (Printed in the U. S.
(Copyright © 1960 by The C. V. Mosby Company)

THALIDOMIDE—A NEW NONBARBITURA SLEEP-INDUCING DRUG

LOUIS LASAGNA, M.D.
BALTIMORE, MD.

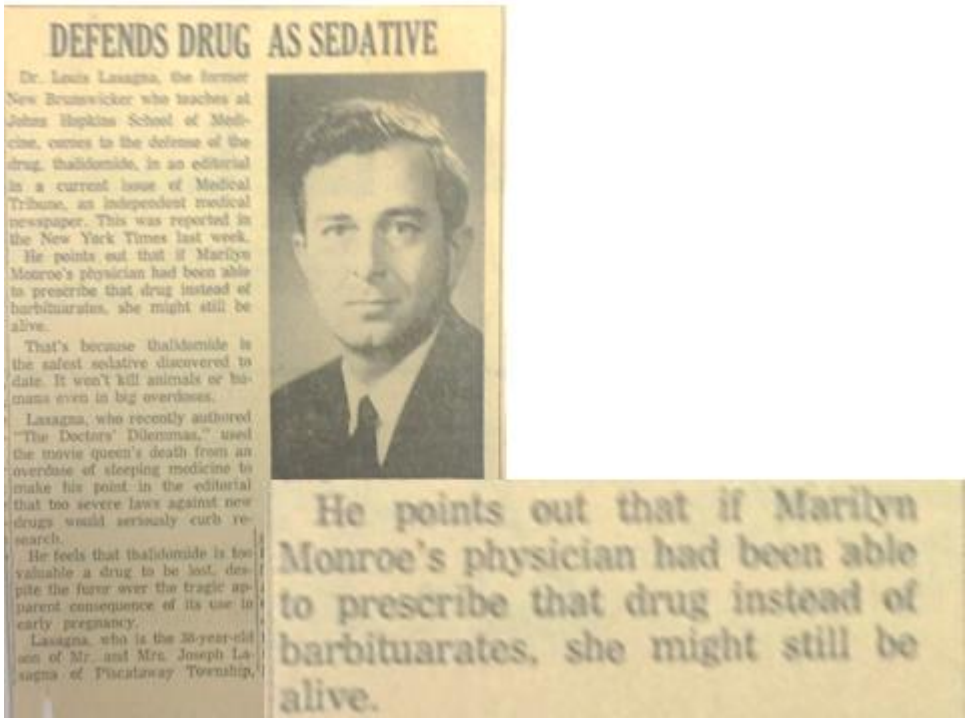
From the Departments of Medicine (Division of Clinical Pharmacology), Pharmacology, and Experimental Therapeutics, Johns Hopkins University School of Medicine

(Received for publication Dec. 9, 1959)

THALIDOMIDE* is the generic name for N-phthalyl-glutamic acid imide, a compound which has been employed in Europe for several years as a sedative-hypnotic. It is chemically related to glutethimide (Doriden), another sedative-hypnotic, and to bemegride (Megimide), a convulsant analeptic.

Because he did this trial, Merrell, the company trying to bring it onto the market over in the States said, “FDA seem reluctant to let us get our drug on the market, why don’t you go in and say you’ve done this controlled trial and persuade FDA to let the drug on the market”. So he did. After his new regulations about controlled trials came into place in 1962 the media got hold of the fact that Lasagna had done a trial on thalidomide and that he had been into FDA lobbying for the drug and they asked him “What’s up Doc?”

Now ten weeks before the 1962 regulations were put in place Marilyn Monroe committed suicide. She overdosed on barbiturates so Lasagna’s stumbling response to the media enquiries was, “Well if Marilyn Monroe had been taking thalidomide as a sleeping pill rather than a barbiturate she’d be alive today”.



DEFENDS DRUG AS SEDATIVE

Dr. Louis Lasagna, the former New Brunswicker who teaches at Johns Hopkins School of Medicine, comes to the defense of the drug, thalidomide, in an editorial in a current issue of Medical Tribune, an independent medical newspaper. This was reported in the New York Times last week.

He points out that if Marilyn Monroe's physician had been able to prescribe that drug instead of barbituarates, she might still be alive.

That's because thalidomide is the safest sedative discovered to date. It won't kill animals or humans even in big overdoses.

Lasagna, who recently authored "The Doctors' Dilemmas," used the movie queen's death from an overdose of sleeping medicine to make his point in the editorial that too severe laws against new drugs would seriously curb research.

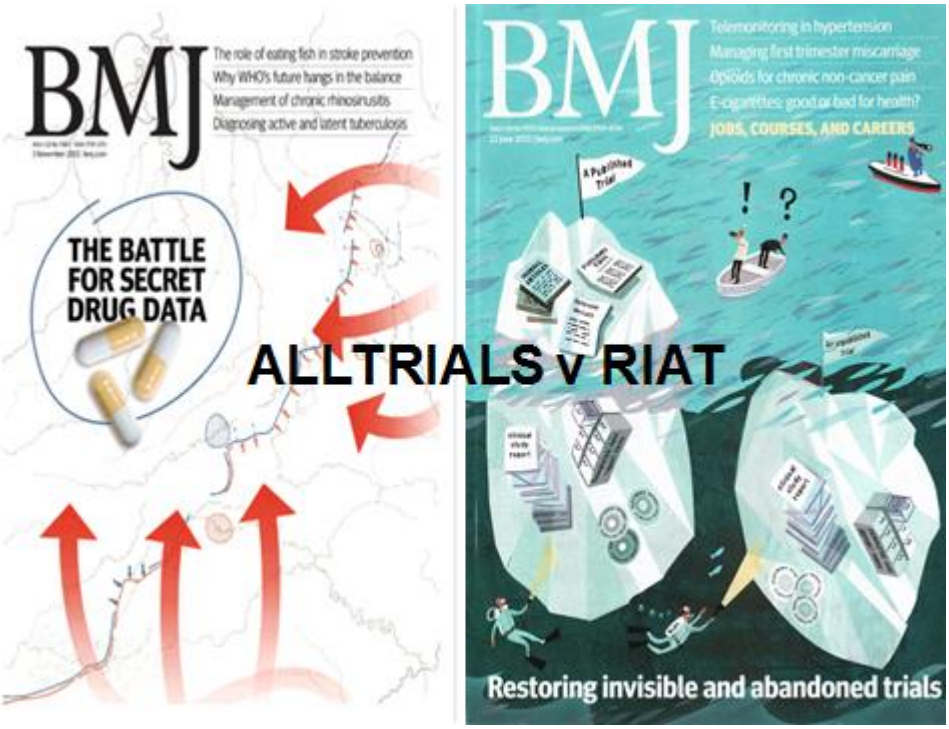
He feels that thalidomide is too valuable a drug to be lost, despite the furor over the tragic apparent consequence of its use in early pregnancy.

Lasagna, who is the 36-year-old son of Mr. and Mrs. Joseph Lasagna of Piscataway Township,

He points out that if Marilyn Monroe's physician had been able to prescribe that drug instead of barbituarates, she might still be alive.

Now this brings us to the denouement, which is this. You’ve seen that the BMJ are trying hard to get access to clinical trial data. If you don’t have the data it’s hard to know what the drug has actually done. You’ve heard of the AllTrials campaign. You may not have heard of RIAT – this stands for Restoring Invisible and Abandoned Trials.

I am part of a consortium trying to RIAT GSK’s Study 329 – one of the most famous clinical trials of recent years. This was a trial of paroxetine in children who were depressed which has a wonderfully distinguished authorship line. It is a ghost written paper, the actual authors aren’t there and the authors who are there haven’t seen the raw data.



LIPPINCOTT WILLIAMS & WILKINS

Journal of the American Academy of
CHILD & ADOLESCENT PSYCHIATRY

Volume 40(7) July 2001 pp 762-772

Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial

[Articles]

KELLER, MARTIN B. M.D.; RYAN, NEAL D. M.D.; STROBER, MICHAEL PH.D.; KLEIN, RACHEL G. PH.D.; KUTCHER, STAN P. M.D.; BIRMAHER, BORIS M.D.; HAGINO, OWEN R. M.D.; KOPLEWICZ, HAROLD M.D.; CARLSON, GABRIELLE A. M.D.; CLARKE, GREGORY N. PH.D.; EMSLIE, GRAHAM J. M.D.; FEINBERG, DAVID M.D.; GELLER, BARBARA M.D.; KUSUMAKAR, VIVEK M.D.; PAPATHEODOROU, GEORGE M.D.; SACK, WILLIAM H. M.D.; SWEENEY, MICHAEL PH.D.; WAGNER, KAREN DINEEN M.D., PH.D.; WELLER, ELIZABETH B. M.D.; WINTERS, NANCY C. M.D.; OAKES, ROSEMARY M.S.; MCCAFFERTY, JAMES P. B.S.

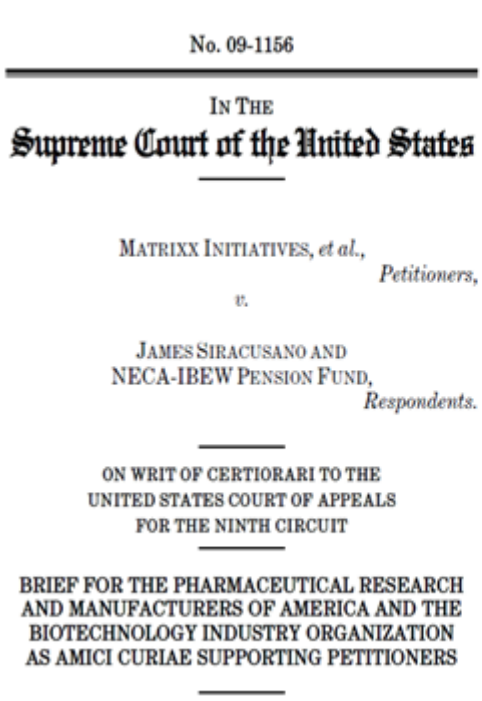
GSK were charged with fraud by New York State for this article after a document came to light which showed that the company's own internal view was that the trial had shown the drug didn't work. But what they were going to do was pick out the good bits of the data, write those up and market the drug on the back of a ghost written article. New York State sued them for fraud, the company settled and this issue was also at the heart of the recent $3 billion fine GSK have paid.

Yet in the House of Commons Clinical Trials document you find GSK lauded the whole way through as a model of transparency.

Well, testing the transparency issue out with colleagues I have been trying to get access to the raw data from 329 and GSK are refusing access to the raw data from 329.

We're trying to do what the US Supreme Court have said investors have a right to do in the Matrix case you see here. This was in 2010. The Supreme Court decided that if you're in an investor in a pharmaceutical company you have a right to see the adverse data from any of the work that has been done within the company and as an investor you have the right to make up your own mind as to what the data actually means.

That judgement stands in complete contrast with what GSK want and what the House of Commons have suggested should happen which is that investors or patients or doctors do not have a right to make their own mind as to what the data actually means.



No. 09-1156

IN THE

Supreme Court of the United States

MATRIXX INITIATIVES, *et al.*,
Petitioners,
v.
JAMES SIRACUSANO AND
NECA-IBEW PENSION FUND,
Respondents.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

BRIEF FOR THE PHARMACEUTICAL RESEARCH
AND MANUFACTURERS OF AMERICA AND THE
BIOTECHNOLOGY INDUSTRY ORGANIZATION
AS AMICI CURIAE SUPPORTING PETITIONERS

We are not in favour of placing anonymized individual patient-level data (IPD) in the public domain in an unrestricted manner…

specific individuals should be provided with controlled access to IPD through carefully managed and secure "safe havens".

Access should be facilitated by an independent "gatekeeper" responsible for insuring that the data … makes a useful contribution to scientific understanding

GSK have been holding out. They want us to go through the mechanism they have written into the House of Commons document to get a look at the data they've got. Despite what the wider world has come to believe about GSK and transparency, they don't want to do give access to the actual raw data. So it's watch this spot.

There two ways to solve a problem – a top down and a bottom up way – or shower and bidet approach.

The shower approach is about the key things that politicians can do for us. They are the ones who can change the game by looking at:

1. the patent status of drugs - are companies being over rewarded?
2. the prescription only status of drugs- is this a safe mechanism or not?
3. the role of access to RCT data.

When people hear the words evidence based medicine, they think we are practising data based medicine – but we aren't. How do Jim and other politicians help us to get to data based medicine.

We are at a critical juncture. There's a trial in the European Court right now on just this issue. Beyond patent rights and data exclusivity rights companies are claiming privacy rights. Abbvie have taken a legal action against the European Medicines Agency's open data policy which was giving researchers and doctors an opportunity to access the data from trials. Abbvie who make Humira, the biggest selling drug in the world, have taken a legal action which has blocked this on the basis that they don't want you to see the adverse events that may have happened in Humira clinical trials.

Shower

Patents
Data Exclusivity

Prescription-only Status

RCTs & Data

Evidence v Data Based Medicine

Privacy Rights

The bidet approach is this. It emphasizes comparative safety rather than comparative effectiveness research. It encourages patient reporting of adverse events and paying much more heed to what patients and doctors combined report than the data from Controlled trials.

It attempts to get people on the right drugs for them because if people are on drugs that we're going to save money and good reporting of adverse events is still the best way to discover new drugs..

Bidet

Data Based Medicine

Comparative Safety Research

Drug Trials

Patient Reporting

Consumer Pressure

[Save Money
New Drugs]

If you take a flight from London to Glasgow or wherever this evening you put your trust in the pilot on the plane. In the same kind of way you put your trust in a doctor when you go on a pill.

Pilots and doctors both report on adverse events. People pay heed to the adverse events pilots report because if you go down the pilot goes down with you. She has a vested interest in making sure that the near miss is taken into account, and the way people respond factors this in. If the authorities didn't make changes, pilots would refuse to fly.

Doctors also reports of crashes and near misses but when they get reported to FDA-MHRA or companies they are discounted. They count for nothing. Current health care is all about trying to indoctrinate doctors not to believe what they see with their own eyes. To go by the supposed Evidence and if the adverse event isn't reported in the evidence it didn't exist. Current health care is all about alienating doctors from patients. We've got to try and return to a world where there is teamwork between doctors and patients.

Today if you suffer an adverse event you have a real problem. We all wonder how we as individuals can fight back on issues like global warming and things like that. We have fought back when it comes to food in terms of the slow food movement.

The place that the fight back happens in medicine – and perhaps on the wider issues through medicine – happens when you walk into a doctor's room and attempt to raise an adverse event. This is an intensely dramatic moment. For the most part you are not going to find your doctor sympathetic. You're going to feel the system that has captured him or her. We have to create the conditions where people can recapture their doctor.

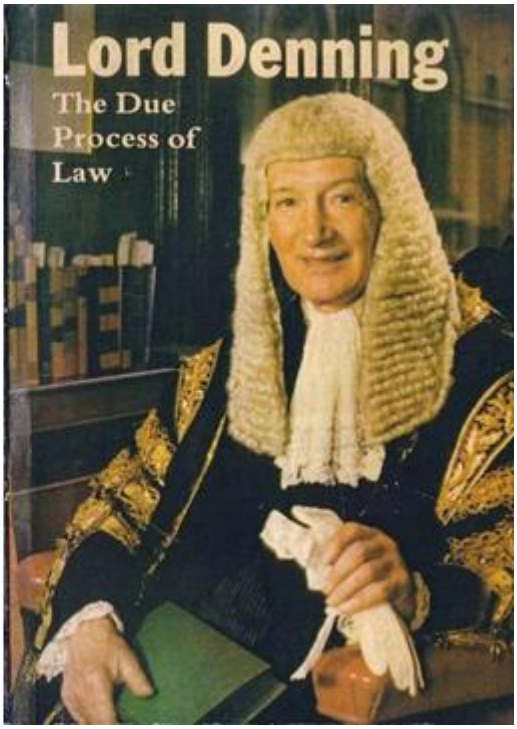
The best metaphor I can find for what happens if you have an adverse event as things stand is that you are an innocent imprisoned. When people affected by statins, who have become dependent on antidepressants, who have had lost a child or partner to suicide on the over 100 drugs that can trigger suicide seek information they find they are bounced from agency to agency – regulator to Dept of Health to Board of Registration – with no-one prepared to acknowledge the possible role of treatment in what has happened.

Being Irish wrongful imprisonment offers a potent metaphor. The Guildford Four and Birmingham Six were two cases of wrongful imprisonment from the 1990s. And Lord Denning's response on the Guildford Four issues typifies how the system will respond to you now if you have an adverse event on any drug – "if your story is right it's such an appalling vista…. ".

THE GUILDFORD FOUR

If their story is right
it is such
an appalling vista
it cannot be

Wrongfully convicted
prisoners should stay
in jail
rather than be freed
and risk a loss of public
confidence in the law.



Jim Dobbins MP:

My situation as chair of this group is to encourage the government to accept that this is a major problem that they have to deal with. People have been suffering for decades and there has to be some way of helping, supporting, counselling and providing services across the country – and I'm not saying in every commissioning group, I'm not saying that at all – but they need some advice, some guidance on this issue. Not only on this issue but on other issues otherwise you're going to get a postcode lottery across the country on all sorts of health issues. I hope the government will be persuaded that they need to have some sort of input into how all that is delivered.