

## 5: TRUSSED IN GUIDELINES

Bill was in his 70s, tall and relatively fit for his age if slightly overweight. His wife was petite. She gave every impression of having been dependent on a physically and behaviorally imposing husband, although their roles were now reversed. Bill had had a stroke a month earlier and Sally was distraught. She was sure that he could recover and concerned that the medical team had not referred him for active rehabilitation. He had shown no signs of recovery of function after his stroke, though. In their opinion there was nothing to build on, but they had asked me to assess if there might be psychological factors or a depression holding him back.

When I saw Bill he had no language. He appeared to be trying desperately to communicate, however, almost like Jean-Dominique Bauby in his Diving Bell. He had something between a cough and an effort to clear his throat that apparently had persisted for weeks. He hacked every few minutes, then fixed me with what appeared to be a pleading look in his eyes. Some patients after a stroke cannot clear saliva pooled in their esophagus, but Bill's hacking was different in its quality and persistence. "Why can't they do something about it", Sally said, "surely they can make him more comfortable".

Bill was on a cholesterol-lowering statin and an ace inhibitor to lower his blood pressure, I discovered. The attending doctor had said it was in line with current international guidelines to put everyone who had a stroke on a statin and an ace inhibitor.

I recommended stopping both treatments: either of these two drugs could have been holding Bill back from making some progress. The statins can cause muscle pain and weakness, which he could not now complain about. If the medical team was planning no more active intervention on his behalf, why not stop the treatment and see? All that guideline-based treatment could do, at best, would be to prolong an agonizing life. As for the ace inhibitor, it was almost certainly causing his hacking cough – this was an unusual but known side effect of this group of drugs.

But guidelines were guidelines, and the medical team was unlikely to go against them. There was no point telling Sally that the hacking could be sorted out. Why set her against the doctors even more than she already was if they were so set in their ways? Generating hostility on their part at betrayal by a medical colleague's interference wouldn't do Bill any good, but it might compromise my ability to make a difference for someone else.

Aside from the horror of this case, few physicians would see anything remarkable in it. An unfortunate medical error in the treatment of this particular patient perhaps, but it's impossible to practice medicine without errors. Better a few have grim outcomes like this than have more lives lost because of a failure to manage patients properly after a stroke.

The problem is, the distress Bill had to put up with so that his doctors could feel comfortable and comply with ostensibly the best available evidence as embodied in the

latest authoritative guideline is fast becoming the clinical norm rather than an exception. There was once only a small number of exceptions, as for instance in the case of vaccination, where medicine was prepared to inflict vaccine-induced injuries on some in the hope that a much greater number would benefit, but this ethos is changing rapidly.

Take Sheila, who had had anxiety and agoraphobia during the 1960s – she would likely have been diagnosed with panic attacks today. She had been caught up for years in what was an almost automatic prescription of benzodiazepines for anxiety and became physically dependent on them. The combination of anxiety and benzodiazepine dependence made her agoraphobic. She was scared to venture out of the house.

When her husband died two decades later, everyone feared she would become dependent on her children. Remarkably, she instead struck out on her own. She bought an apartment, some distance from any of her children, and began socializing in a way she had not done for over two decades.

When the alarm was raised in the 1980s about benzodiazepine dependence, many primary care physicians changed their patients to low doses of antipsychotics or antidepressants instead, and Sheila's new doctor was no exception.

I first met Sheila around the time that the selective serotonin reuptake inhibiting (SSRI) antidepressants came on stream. Her doctor referred her to me for review of her medications. Rather than the combination of an antipsychotic and antidepressant she was

on I started her on an SSRI. At first, she did much better. But shortly afterwards she began grinding her teeth. We changed her to another SSRI. Again she initially did well, but then the grinding and restlessness commenced again. The same happened with each of the four SSRIs then available.

Sheila's teeth grinding was so intensely painful that she had to remove her dentures. With her teeth out she became more self-conscious, and grew more reclusive. She was slipping back into the shell in which she had lived for over 20 years. I opted to go back to one of the older antidepressants which, in a low dose, made her less anxious without causing teeth grinding and restlessness. We met regularly thereafter for close to 10 years during which time she maintained a delicate equilibrium.

Then, at the age of 80, she had a "turn" and was brought to hospital. There were some inconclusive changes on her cardiogram, possibly indicative of a minor heart attack, and Sheila came out of hospital on both an SSRI and a statin. The SSRI had been prescribed by the hospital medical team because it was supposedly safer for the cardiovascular system than her older antidepressant; the statin because international guidelines now recommend statins for everyone who has had a cardiac event – regardless of whether the person's cholesterol levels are high.

Sheila now developed two sets of problems. Her teeth began to grind again and her legs became so weak and painful that she fell when she least expected it, so she couldn't go out to the shops or to see friends. I was asked to see her. I suggested stopping the statin

as it was probably causing the weakness and pain in her legs, and switching her back to her previous antidepressant. Her primary care doctor was faced with a choice between my advice and the input from the medical team. He opted to continue the statin and SSRI prescriptions. The calculation he apparently felt called on to make was whether it was better to keep her alive, although disabled by treatment, or give her a better quality of life but risk her dying earlier than she would otherwise have done.

For over twenty years I have copied my patients on all correspondence that concerns them. Sheila had the letters to her doctor recommending he stop her SSRI and statin. Although she told me that she was sure I was right about the drugs, she didn't demand her doctor do what I recommended. She was nervous that in her current frail state she might suddenly have a medical emergency and would be critically dependent on him. She had a niggling doubt that he might not be as quick to help her if she were a difficult patient. She was a hostage – as many patients are.

Her doctor was finally persuaded that SSRIs were no better for the cardiovascular system than her older antidepressant and might actually increase her risk of a stroke especially when combined with the aspirin she was on. Switching antidepressants improved her tooth grinding and her restlessness. But Sheila never recovered. The statin was still prescribed and her leg pains and weakness remained. Unhappy and lonely, she ended up in a residential home.

Sheila's doctor never let pharmaceutical company sales reps into his practice. He had no dealings with industry. Yet here he had been doing exactly what industry would have wanted – and seemingly oblivious to the obvious difficulties his patient was having in front of his eyes. The problem he had and the biggest problems Sheila and Bill faced had a common source: sets of guidelines produced by medical organizations, in both America and Europe, in the hope that these guidelines might improve medical care and provide a bulwark against company marketing. But these same guidelines have instead too often become a means to harness the medical impulse to give the best possible care to the delivery of the latest drugs, even when these offer fewer benefits and more harms than older treatments.

### **THE END OF DISCRETION**

As 2009 closed a controversy erupted across the pages of medical journals concerning Tamiflu (oseltamivir), an antiviral drug produced by Roche pharmaceuticals, who had had several years of good fortune as Western governments stockpiled the drug, fearing a pandemic first of avian flu and then of swine flu. The published evidence appeared to indicate that Tamiflu reduced the likelihood of a full-blown influenza, reduced the length of a flu episode that developed and reduced the secondary complications of influenza, such as pneumonia or other respiratory disorders that might lead to hospitalization and even death in vulnerable groups. This led national governments throughout the Western world, and agencies like the Center for Disease Control in the United States, to a set of recommendations to doctors on the management of flu that hinged on a widespread use of Tamiflu. The trouble was, no-one could access the data on which these recommendations

were made. Furthermore, it became increasingly clear that only a fraction of the trials that had been undertaken were published, and of those published, ghostwriters had played a significant role in what was reported

<sup>212</sup>. The more material leaked into the public domain, the less effective Tamiflu looked, and the more dangerous using it began to seem – it appeared to induce neurological problems in a subgroup of patients and to make others suicidal. But a further dilemma came into view – governments had spent billions on this drug. Would they admit they had spent billions on a drug for which they had seen only a portion of the evidence and that might not work as designed? Would they pressure Roche to release all the data on the drug?<sup>213</sup>

Sequestering data violates a basic norm of science even if it is overlooked by law. Today when public policy at many levels is or aspires to be based on scientific data, such violations have ever greater ramifications, from the individual treatment our doctor gives us to decisions about national and international health care. To see how hiding medical data directly affects the doctors we consult and the quality of medical care we receive, we need to explore two aspects of everyday medical practice, the increasing use of guidelines and what they are based on (the subject of this chapter) and the interests behind the measurement technologies to which practitioners like Dr N, who we met in the introduction, turn (the subject of the next chapter).

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<sup>212</sup> Deborah Cohen, *Complications: Tracking down the data on oseltamivir*, *BMJ* 339, 1342-1347 (2009); Peter Doshi, *Neuraminidase inhibitors: the story behind the Cochrane review*, *BMJ* 339, 1348-1351 (2009).

<sup>213</sup> Fiona Godlee, *We want raw data now*, *BMJ* 339; b5405 (2009).

The evolution of guidelines is best told first hand. For that reason we will focus on guidelines for the treatment of mental health disorders, but the story that unfolds here parallels developments in other areas of medicine – and it is these developments that ensnared Bill and Sheila. In every area of medicine, doctors increasingly find they have to take into account guidelines or standards that have been established, not infrequently to the detriment of the patient in front of them. It is against such guidelines that medical personnel are ever more likely to be judged by the managers of the service they work in or by the legal system should one of their patients take an action against them.

Our point of entry into the story lies in 1993 when the Janssen pharmaceutical company was hoping to bring their new antipsychotic Risperdal (risperidone) to the market. An FDA review of this drug prior to its launch stated: ‘We would consider any advertisement, promotion or labeling for Risperdal false, misleading or lacking fair balance under Section 502 of the Act if there is a presentation of data that conveys the impression that risperidone is superior to haloperidol or any other marketed antipsychotic drug product with regard to safety or effectiveness’<sup>214</sup>.

All of the antipsychotics developed during the 1990s, from Risperdal through to Lilly’s Zyprexa, Astra-Zeneca’s Seroquel, Pfizer’s Geodon and Bristol-Myers Squibb’s Abilify (among others), had been tested in pre-marketing trials against haloperidol, one of an earlier generation of now off-patent antipsychotics. In their trials all of the companies

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214 Andrew Mosholder, *Review and evaluation of clinical data, application NDA # 20-272 (11th May 1993)*. Cited in: Robert Whitaker, *Mad in America* ( Boston : Perseus Publishing, 2001).



used a higher dose of haloperidol than clinically needed<sup>215</sup>. The stated rationale for using haloperidol as the comparison drug was that it was supposedly the market leader. The unstated rationale was that given the side effect profile of the newer drugs they stood their best chance of looking good from a marketing point of view if compared to high dose haloperidol. This kind of comparison is standard company practice for bringing any new drug to market, whether statins, antihypertensives, pain-killers, treatments for osteoporosis, or for gut problems – compare yourself to some formulation of an older compound against which the new drug is already known to look good on some parameter.

On the face of it, FDA's cautionary note, repeated for subsequent antipsychotics, and in slightly different form for cholesterol lowering statins, proton pump inhibitors for gut disorders, the latest antihypertensives, the Cox-2 inhibiting painkillers, or biphosphonates for osteoporosis, looks like it should produce problems for any company wishing to market new drugs that, like Risperdal, can cost up to 50 times as much as older drugs.

There are lots of ways to get people to take a new drug that may be no more effective than an older one, however. For one thing new drugs come with a hope of superior efficacy built in that older drugs have lost, so we want them. But how to price up this hope – is 25 or 50 times the price of older drugs when the new drug is no better than the old drug for the same malady the right answer? Patients trade on such hopes, and one approach companies now take is to set up patient groups to lobby for the new drug. Such groups are all too willing to believe they are being denied access to the latest and best treatment on cost-cutting grounds. And it is difficult for doctors, or more importantly

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215 David Healy, *The Creation of Psychopharmacology* (Cam. Ma: Harvard University Press, 2002).

these days, politicians or insurance companies to resist articulate patients who question whether they are being denied the newest and best treatments on the basis of economic rationing. Doctor, what would you give to a member of your own family?

Patient hopes and expectations work in favor of a pharmaceutical company bringing a new drug to the market, but in addition since the 1990s, doctors in many countries, whether they work for a health maintenance organization or in a universal healthcare system, have also had to adhere to drug formularies (lists of approved drugs) which dictate what they can and cannot prescribe. These formularies arose in response to perceptions that healthcare costs were escalating uncontrollably and that a key element in this escalation was the price of drugs. The formularies often start with a principle – that, where possible, doctors should prescribe cheaper generic rather than higher cost branded compounds. The guidelines are intended to be both evidence-based and cost-sensitive – with some trade offs, so that if a new drug cost more but could show a real benefit over older agents, for example, it would be included on the approved list. The types of assessments pharmacists and doctors with no links to industry would make in constructing formularies, it was thought, would in general slow the entry of unnecessary new drugs to the market.

When it came to managing costs, from the 1990s onwards service managers and others could, at least in theory, also turn to health economics to assess company claims that their new drugs offered good value for money. And of course if the market really was a free market and several different companies each brought to market new antihypertensives or

treatments for osteoporosis, competition should drive the price of the new drugs down – as many from Senator Kevaufer in 1962 onwards have argued<sup>216</sup>. But this has never happened.

In the 15 years following the FDA ruling on Risperdal and other new antipsychotics, no independent evidence appeared that any of the newer antipsychotics was superior to the older ones in terms of either safety or efficacy—even though the new treatments cost between 50 and 80 times as much<sup>217</sup>. But in the interim the companies managed to convert virtually everyone in the medical community from older to newer antipsychotics, and all of the new drugs made it on to hospital formularies – how? More generally, how do the pharmaceutical companies manage to market newer drugs so successfully when the cost of healthcare is forcing everyone to be cost aware and in the face of guidelines, which presumably based on the evidence are going to come to the same conclusion as FDA?

Part of the answer to this conundrum lies in the medical academics who, as we have seen, are among the key people who influence a doctor’s view of particular drugs. Regulators have no control over what these academics say – academics, often, whom pharmaceutical companies have made into opinion leaders. In the case of antipsychotics like Risperdal, statins like Lipitor or proton pump inhibitors like Nexium, professors of medicine, psychiatry, pharmacology or general practice can say what they like in lectures, or report

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216 Richard Harris, *The Real Voice* (New York: MacMillan, 1964).

217 Robert Rosenheck et al., *Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: A randomised controlled trial*. JAMA 290, 2693-2702 (2003); Jeffrey A. Lieberman et al., *Effectiveness of antipsychotic drugs in patients with chronic schizophrenia*, New England Journal of Medicine 353, 1209-1223 (2005); Peter B. Jones et al., *Randomized Controlled Trial of the effect on quality of life of second vs first generation antipsychotic drugs in schizophrenia*, Archives of General Psychiatry 63: 1079-1087 (2006).

what they like in medical journals. Companies can even include statements in their adverts claiming that, say, Risperdal is superior to haloperidol, provided it is clear the statement has been made by an academic rather than the company. There will be a footnote in the advert to a medical article in which superiority is claimed – almost certainly a ghostwritten article.

An even more effective marketing technique is to coax support from medical academics who are not hired guns, who may even see themselves as hostile to company marketing and keen to constrain this marketing within a framework of independent treatment guidelines. It is in fact by manipulating the most independent of medical academics through guidelines that companies have been able to make new drugs from Risperdal to Lipitor, Vioxx, Nexium and Fosamax into the most profitable drugs in the world.

### **Consensus Conferences**

In the 1980s it seemed obvious to many medical academics with no links to the pharmaceutical industry that where there was a dispute about a drug or other medical treatment it made sense to bring representatives of the differing points of view together in an attempt to achieve consensus. This led to the creation of consensus conferences aimed at producing guidelines for clinical practice<sup>218</sup>. Initially, these consensus conferences seemed like a way to rein in the excesses of pharmaceutical company marketing departments – if we review all the evidence it will surely be clear that the benefits of a new drug are far less than the marketing hype might suggest. With this in mind, groups

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218 Trevor A. Sheldon and George D. Smith, *Consensus conferences as drug promotion*, *Lancet* 341, 100-102 (1993).

across medicine began to convene conferences to produce treatment guidelines on new drugs for conditions ranging from arthritis to schizophrenia.

Initially, the organizers of these consensus conferences were in the business of developing guidance for doctors rather than guidelines to be rigidly adhered to. Twenty years later the guidelines we now have still notionally offer guidance to doctors, but this is the kind of help that once led Ronald Reagan to suggest that the scariest words in the English language were “I’m from the Government and I’m here to help you.”

By the time I was invited to a consensus conference in London convened by Catalyst Healthcare Communications Ltd on behalf of the Janssen pharmaceutical company in 1995, drug companies far from feeling constrained by guidelines had begun to embrace them. Other invitees to this London meeting included senior psychiatrists, pharmacists, and economists. No-one among the invitees would have been thought of as a friend of the pharmaceutical industry. We were presented with the published results of Janssen’s trials of Risperdal. There was no attempt to stifle debate or to block us from bringing in any relevant material we might have been aware of.

The exercise involved taking the published research on Risperdal and discussing what would happen in real life if the results found in the clinical trials, which had all been reported in the better journals, applied. What effect would it likely have on the rate patients got discharged from acute hospital settings or from longer-term care facilities and on their rates of readmission to a hospital bed? When costing the outcomes a

significantly higher cost was used for Risperdal compared to the older drugs.

Nevertheless, use of Risperdal came out as less expensive compared with older drugs in the long run. This result didn't make sense to me and was at odds with everything I saw about the use of Risperdal in clinical settings, where those taking Risperdal should have clearly been doing better if this "finding" was a real one.

Looking at how Catalyst pulled off this trick, it became clear that companies can almost guarantee an outcome like this. The reason: the bedrock on which guidelines depend is the published evidence from company clinical trials. If a guideline is going to be credible, its proposers should have access to all relevant trial data - exactly what the companies appeared to offer (but didn't). With this assumption, advocates of evidence-based medicine would think that, based on the data, the individual bias of participants or collective bias of the group or any bias stemming from the fact that these were company trials should have little effect on the final conclusions. A group of radiologists, doctors free of drug company influence, or even hostile to industry but prepared to go by the evidence, should come to much the same conclusion on Risperdal as our consensus group - that switching patients from older drugs to Risperdal would save money. This consensus-group meeting resulted in a publication claiming that treatment with Risperdal offered value for money<sup>219</sup>. It was followed over the next few years by publications on results from similar exercises undertaken with Zyprexa and other antipsychotics<sup>220</sup>.

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219 J.F. Guest, W.M. Hart, R.F. Cookson and E. Lindstrom, *Pharmacoeconomic evaluation of long-term treatment with risperidone for patients with chronic schizophrenia*, *British Journal of Medical Economics* 10, 59-67 (1996).

220 Stephen Almond and O O'Donnell, *The cost-effectiveness of olanzapine compared to haloperidol in the treatment of schizophrenia in the UK*. Final report prepared for Lilly Industries, Personal Social Services Research Unit, University of Canterbury (1996), published in *PharmacoEconomics*, 17 383-389 (2000)..

Slightly over a year later I was invited to another consensus conference, again linked to Janssen and Risperdal. The procedure was the same. We had all been sent a dossier with all the published Risperdal trials, and trials of other new antipsychotics. Any other information we asked for was forthcoming. Based on this material, we were asked what would be the optimal and cost-effective first line treatment for patients with schizophrenia in chronic care and other treatment settings. Again based on the clinical trial data, Risperdal looked good and “our findings” were presented under our names at major international psychopharmacology settings<sup>221</sup>.

Pharmaco-economic evaluations like that of our consensus group were, at least on the surface, aimed at costing medical procedures to determine which offered value for money. A few voices at the time were saying that we in medicine couldn't do what the economists were purporting to do – that too little was understood about what really goes on in medical care. But it seemed clear the pharmaceutical industry was going to pull this new discipline into existence. Drugs function within healthcare the way automobiles do in the wider economy – they can be costed while the degradation of the environment or of medical care remains unmeasurable and uncostable.

Before getting involved in any of these consensus conferences, I had committed myself to the position that pharmaco-economics was bogus science in a debate over claims that the first of the new antipsychotics, Clozaril, which had been launched in 1989 with a price tag of roughly \$10,000 per year, compared with \$100 for the older drugs, was

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221 Ann Mortimer et al., *Consensus statement on schizophrenia standards in care for maintenance therapy and poorly responding/treatment intolerant patients*. CINP meeting. International Journal of Neuropsychopharmacology 1, Abstracts Supplement (1998).

nevertheless cost-effective<sup>222</sup>. It was clear at the time that Clozaril had set a price benchmark that, if it did not meet significant resistance, would become the price norm for any subsequent new antipsychotics coming on the market, with major economic consequences for individual patients and health systems in general.

As part of company marketing strategies, economic evaluations of antidepressants also began to come on stream in the 1990s. These purported to show that despite a price of \$1000 per year for a drug like Prozac, compared with the \$100 (or less) tag for older drugs, the new drugs represented value for the money<sup>223</sup>. Along with colleagues, I had argued that such prices were even more likely to lead to serious adverse financial consequences for the health services than the even bigger mark-up on antipsychotics because so many more people were prescribed antidepressants<sup>224</sup>. This seemed obvious, but no one else was saying it. In the face of publications in leading journals claiming the SSRIs or other new treatments would produce savings, there was no dissent.

Given my published positions, it is interesting that company personnel felt confident asking me along to a meeting on economic evaluations and consensus guidelines.

Ironically, a few years later, when an independent expert for Britain's National Institute for Health and Clinical Excellence (NICE) suggested consulting me on the antidepressant guidelines NICE were constructing, the idea was shot down on the basis that Healy was too anti-corporate when it came to drugs. Too anti-drug-company for NICE, but just perfect, it seems, for pharmaceutical companies.

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222 David Healy, *Psychopharmacology and the ethics of resource allocation*, *British Journal of Psychiatry* 162, 23-29 (1993).

223 Donald Eccleston, *The Economic Evaluation of Antidepressant Drug Therapy*, *British Journal of Psychiatry* 163, Supplement 20 (1993).

224 Ffion Johnstone, Ian Rickard and David Healy, *The costs of psychotropic medication*, *British Journal of Psychiatry* 167, 112-113 (1995).



Why go to meetings like this? It paid. For many outside observers, the repeated endorsement of on-patent products over older drugs at guideline meetings is close to inexplicable. Finding that the participants at these meetings have at some time been paid by a pharmaceutical company seems the only way to account for this. How else can you explain, for instance, the fact that in these guidelines Healy seems to be endorsing things when he has in other places appeared to say the opposite?

Another factor is lots of us want to be where the action is and industry is very good at creating action or at least the appearance of action. A further factor is friendship. Put in rooms for meetings like these, even people who have been on the opposite sides of arguments in print tend to get on. If others seem friendly in the flesh, it's somehow easier to see where they're coming from or to find a way to reconcile views. Companies excel at cultivating friendships – remembering details about you and making you feel that you count. Besides, as the taint of working with industry has receded, and as more and more people are linked in, there increasingly seem to be fewer and fewer differences between “them” and “us”. This is a world in which conflict of interest becomes a badge of honor, the more links to the greater number of companies the better.

These are all important issues but the conflicting interests of payment, friendship or boredom do not explain what happens. Here's a further puzzle - the guidelines emanating from company-sponsored meetings are all but indistinguishable from those

produced by committees with no links to Pharma. Whether the game is played by free market rules or within a socialized system, Pharma wins.

### **ONE GUIDELINE, ONE VOICE**

To bring out how companies manage to win regardless of which way the game is played, let us contrast practices in the United States and Britain, in particular the operations of the British guideline system run by the National Institute for Health and Clinical Excellence (NICE), widely regarded as the most independent guideline system in the world, and the American Texas Medication Algorithm Project (TMAP)<sup>225</sup>. TMAP was created by industry. NICE was set up in part to contain industry and has the distinction of having been sued by companies for advising against current drug treatments for Alzheimer's disease. NICE is exactly the kind of system that the Obama administration looked to put in place as part of its healthcare reform package<sup>226</sup>.

TMAP was set up in 1994 the year after Risperdal was launched in the United States. The project was initially funded by Janssen, but soon thereafter all of the other major pharmaceutical companies had signed on as well. TMAP started with a panel of experts convened to produce a consensus on the use of antipsychotics. Later panels were pulled together to consider the use of antidepressants and mood-stabilizers. Many of these consultants had prior links to Janssen and other companies operating in the mental health

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225 See Dwight McKee and Allen Jones v Henry Hart, Sydni Guido, Wesley Rish, Albert Masland, James Sheehan and Daniel P. Sattelle, CIVIL ACTION No: 4:CV-02-1910, in the United States District Court for the Middle District of Pennsylvania; M. Petersen, *Making Drugs, Shaping the Rules* (2004); *Big Pharma is eager to help States set medication guidelines*, New York Times, Section 3, pages 1 and 10, Sunday February 1st

226 Timothy Kendall, Linsey McGoey and Emily Jackson, *If NICE was in the USA*, Lancet DOI:10.10116/5c E (2009); Fiona Godlee, *NICE at 10*. BMJ 338, 344 (2009).

field, but these experts were distinguished psychiatrists and psychopharmacologists, and none have complained about having data withheld from them.

The first set of TMAP guidelines concluded that the recently launched antipsychotics - Risperdal, Zyprexa and Seroquel - were the drugs of choice for schizophrenia. A second set of guidelines concluded that rather than older, cheaper antidepressants, the more recently launched on-patent Prozac, Paxil, and Zoloft were now the drugs of choice for depression. Further guidelines moved on to endorse mood-stabilizers such as Depakote over other treatments for bipolar disorder. In each case the guidelines recommended newer drugs as safer, more effective and better tolerated than older agents. In 1999 TMAP commissioned a set of guidelines for the management of childhood mental disorders, even though at the time no psychotropic drugs had been licensed for use in children or teenagers<sup>227</sup>.

In a number of US states, Texas among them, legislators have the power to rule that guidelines such as TMAP's must be applied in the care of any patients receiving treatment in public facilities. The logic is that evidence-based guidelines, if they really do reflect reality, can be expected to be cost-effective over time. The legislators in Texas meet infrequently, are poorly paid, and are intensively lobbied. Perhaps because of such lobbying, or because pharmaceutical lobbyists were able to show the legislators position papers endorsed by experts, in 1999 the state of Texas endorsed, with no dissenting

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227 Carroll.W.Hughes et al, *The Texas children's medication algorithm project: report of the Texas consensus conference panel on medication treatment of childhood major depressive disorder*, Journal of the American Academy of Child and Adolescent Psychiatry 38, 1442-1454 (1999).

views, the TMAP guidelines for schizophrenia, mood disorders and for children, thus requiring state hospital doctors to prescribe the newer drugs first.

The TMAP guidelines were subsequently adopted by executive decision in a large number of other states<sup>228</sup>. In this way companies have effectively produced a situation in which a growing number of patients on Medicaid and other programs end up being put on and maintained on the newest and most costly of their drugs.

The consequences are worth looking at. In 2004, 8<sup>th</sup> graders in Pflugerville, Texas were screened by psychologists. Aliah Gleason, a 13-year old, ticked the box for suicidality on one of the tests – probably a probe such as have you ever wished you were dead. Even though she was regarded as a live wire in class, this tick led to a referral to a psychiatrist, and removal from her family by the child protection services. She was admitted to Austin State Hospital and within hours she was receiving the very best treatment – and did so for the next 9 months. This involved all the latest antipsychotics, antidepressants, and mood-stabilizers, as mandated by TMAP, costing a small fortune. These were administered not individually but in cocktails of up to 5 different medications daily. She gained huge amounts of weight, developed a range of side effects, and showed no evidence of progress. It took 9 months for her family to get her back, and begin to get her off treatment<sup>229</sup>.

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228 These guidelines went on to be adopted at some point by Pennsylvania, California, Colorado, Nevada, Illinois, Kentucky, New Mexico, New York, Ohio, South Carolina, Maryland, Missouri, and Washington D.C., or by jurisdictions within those states.

229 RobWaters, *Medicating Aliah*, Mother Jones, pp50-55 (May/June 2005).

Between 1997 and 2004, Texas Medicaid spending on antipsychotics rose from \$28 million to \$175 million. In the months of July and August 2004, over 19,000 adolescents in Texas were given antipsychotics, even though pharmaceutical companies had not applied for licenses to market these drugs for use in minors.

In 2003, Zyprexa pulled in \$4.3 billion in sales in the US, 70% of which came from state health insurance and other public health programs. It will probably come as no surprise that within all the major companies there are divisions aimed at maximizing the effectiveness of company marketing in the public sector. And it may be no accident that, in 2009, research revealed that children being treated under Medicaid were 4 times more likely to get antipsychotics than children not covered by Medicaid<sup>230</sup>.

Surely nothing similar could happen within Britain's socialized system of medicine, where the key guidelines are produced by NICE, which had been set up with a brief to make recommendations as to the most cost-effective treatments for both physical and mental illnesses? The panelists framing NICE guidelines, whether for cardiac treatments, arthritis management, or psychiatric conditions have access to the resources of the Cochrane collaboration, the independent organization set up by Iain Chalmers initially in Britain but now with centers in all Western countries that systematically reviews the published evidence – taking pains to obtain all the published evidence, and eliminate all evidence that has been duplicated to inflate artificially the apparent benefits of one drug over another. When assembling guidelines, NICE also ensures that it has a range of non-

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230 Duff Wilson, *Poor Children likelier to get antipsychotics*, New York Times, Dec 12th. 2009.  
[http://www.nytimes.com/2009/12/12/health/12medicaid.html?\\_r=2&scp=1&sq=antipsychotics&st=cse](http://www.nytimes.com/2009/12/12/health/12medicaid.html?_r=2&scp=1&sq=antipsychotics&st=cse)

medical participants to balance out any bias the doctors involved may have in favor of the latest treatment.

Despite this, the 2002 NICE guidelines for the use of antipsychotics came to the same conclusions as TMAP: newer agents like Risperdal and Zyprexa should be used before older ones<sup>231</sup>. Lilly responded to this news by incorporating symbols of NICE, and NICE statements into its adverts for Zyprexa, which was now supposedly a medication NICE endorsed. NICE had done for Lilly what we've seen the FDA had indicated would be illegal in the United States for the company to do for itself.

How come? The first point is that while NICE had access to all the published evidence through the resources of the Cochrane collaboration, this really didn't amount to any more than they would have been provided by the pharmaceutical companies had they asked. The Cochrane Center had made it clear that there was a great deal of duplicate publication. The four initial trials of Zyprexa in schizophrenia for instance had given rise to 243 publications of one sort or another – almost entirely company written<sup>232</sup>. While whittling the publications down to establish just how many trials there had been did help to qualify the apparent benefits of Zyprexa, it made no difference in NICE's overall evaluation.

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231 National Institute for Clinical Excellence (NICE), *Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia*. 2002 Technology Appraisal Guidance 43, June 2002. available on [www.nice.org.uk](http://www.nice.org.uk)

232 L. Duggan et al., Olanzapine for schizophrenia, Cochrane Database of Systematic Reviews Issue 2. Art. No.: CD001359. DOI: 10.1002/14651858.CD001359.pub2. (2005)

What might have made a difference lay elsewhere in the vast amount of data from the four Zyprexa trials that simply could not be found in any of the 243 publications – there was nothing on suicides, diabetes, or cholesterol and little on weight gain. Not one publication hinted that patients given Zyprexa in these trials for schizophrenia had the highest suicide rate in clinical trials history; suicide was in fact rare in schizophrenia before the advent of the antipsychotics<sup>233</sup>. Not one publication mentioned that patients in these trials went on to develop diabetes at a rate triple the background rate in the general population, when diabetes was almost unheard of in schizophrenia before the antipsychotics<sup>234</sup>. The publications concealed the extent of weight gain in the patients given Zyprexa, whose weight often ballooned by anything from 20 to 140 lbs. These and subsequent publications also failed to reveal that, regardless of diagnosis, Zyprexa raised cholesterol levels more than almost any other drug in medicine –though Zyprexa had received a patent in part based on company claims that it would be less likely than other antipsychotics to raise cholesterol levels.

The figures for suicides, cholesterol and diabetes were all buried in reports submitted by the company to the FDA. Even furnished with these reports to the regulator, it is difficult to establish what the true figures are and a good deal of data seems to be missing<sup>235</sup>. But NICE and TMAP didn't have the data and didn't even have these reports that were submitted to the regulator – they were working only from the published evidence. Based on a thorough assessment of the publications alone, NICE came to the conclusion the

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233 David Healy et al., *Lifetime suicide rates in treated schizophrenia: 1875-1924 and 1994-1998 cohorts compared*. *British Journal of Psychiatry* 188, 223-228 (2006).

234 Joanna LeNoury et al., *The incidence and prevalence of diabetes in patients with serious mental illness in North West Wales: Two cohorts 1875-1924 and 1994-2006 compared*. *BMC Psychiatry* 8: 67. doi:10.1186/1471-244X-8-67 (2008).

235 This statement is based on my access to the data submitted to the Canadian regulator as part of a legal action on the patenting of Zyprexa.

newer antipsychotics were no better than older agents. But the published evidence still suggested the new drugs provided a better quality of life and a lower burden of side effects than the older drugs, whereas the raw data point to just the opposite conclusions.

Against this background, NICE also had to manage a dynamic situation. First, how would clinicians and patient lobby-groups, who had been bombarded for years with hundreds of publications extolling the virtues of Zyprexa and Risperdal and claiming these drugs liberated patients from some of the terrifying problems caused by the older agents, respond to a recommendation from NICE to use older drugs – had they chosen to give it? The 243 Zyprexa publications and further hundreds from the other new antipsychotics (Risperdal, Seroquel, Abilify, Geodon) played a great part in generating this pressure. Some of the panelists may privately have thought the older drugs were as good as the new ones, but it was difficult to offer evidence for this point of view, especially since they had no access to some of the most telling data. If NICE had come down favoring the older drugs, company-sponsored patient groups, told they should have the older drugs, would likely holler rationing, and even use this supposed rationing as an argument for de-socializing healthcare. Second, just as journals do not publish articles critical of Pharma for fear of a legal action, so also NICE knew it stood to be dragged into a legal action if it came to a decision that was not based on published evidence. And since then, in the case of guidelines for Alzheimer's disease, it has found itself sued even though its decision is based on the published evidence. Rumor has it that NICE was also faced with a British government that was in receipt of communications from several



pharmaceutical companies threatening to pull out of the UK if the guidelines were not favorable to its products<sup>236</sup>.

The NICE guidelines came out in 2002. Three years later two large independent studies, one American and one European, were published showing that older antipsychotics were as effective and tolerable as any of the newer agents, and superior to some of them<sup>237</sup>.

But if a doctor wanted to follow the evidence and prescribe one of the older agents, she would have found a series of guidelines standing in her way, as these are only updated periodically.

### **THE GREATEST DIVIDE IN ALL OF MEDICINE**

Having been invited to a number of guideline meetings, I had a chance in 1997 to convene one. As the Secretary of the British Association for Psychopharmacology, I organized the first consensus conference to look at issues surrounding the prescription of psychotropic drugs to children. The growing number of prescriptions being written for ADHD (attention-deficit-hyperactivity-disorder) had triggered the meeting, but on the day, the treatment of depression in children was the primary focus of attention.<sup>238</sup>

There was an important difference between this and pediatric guideline meetings that came later. In 1997, except for ADHD, there were few published clinical trials.

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<sup>236</sup> This is based on conversations with some of those involved in the process.

<sup>237</sup> Jeffrey A. Lieberman et al., *Effectiveness of antipsychotic drugs in patients with chronic schizophrenia*, *New England Journal of Medicine* 353, 1209-1223 (2005); Peter B. Jones et al., *Randomized Controlled Trial of the effect on quality of life of second vs first generation antipsychotic drugs in schizophrenia*, *Archives of General Psychiatry* 63, 1079-1087 (2006).

<sup>238</sup> David Healy and David Nutt (1997), *British Association for Psychopharmacology Consensus on Statement on Childhood and Learning Disabilities Psychopharmacology*. *Journal of Psychopharmacology* 11, 291-294 (2006).

Furthermore when it came to depression, the clinical wisdom as of 1996 was that unhappiness in childhood was not the same as depression in adults – it was not something for which pills were the accepted answer. As a result when authoring the final document, the premium was on treating the child rather than the condition. Clinicians were recommended to lay out all the treatment options – drug and non-drug – for patients and their parents and if the first treatment didn't seem to be working they were advised to switch to alternate treatments even if not among those the doctor preferred. This was guidance rather than a guideline.

One feature of the meeting became intriguing later on. I had invited all panelists and a number of pharmaceutical companies. SmithKline Beecham were present as were a number of the clinical investigators for Study 329, SmithKline's trial of Paxil in depressed children outlined in the last chapter. This study had been completed at the time the guidelines were written but I didn't know about it and possibly very few others did and there was not a single mention of any Paxil study on the day of the meeting.

Two years later, in 1999, TMAP issued guidelines endorsing the use of SSRIs in children who were depressed<sup>239</sup>. By this time a trial of Prozac in children had been reported and it was known that several other trials were underway. In 2002, the FDA endorsed Prozac for treating depression in children. FDA had also issued a tentative approval to GlaxoSmithKline for the use of Paxil in children, and was likely to do so for Zoloft. An article that had appeared in *Newsweek* to coincide with World Mental Health day in 2002

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239 Carroll W. Hughes et al, *The Texas Children's Medication Algorithm Project: Report of the Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder*, *Journal of the American Academy of Child and Adolescent Psychiatry* 38: 1442–1454 (1999).

claimed there were 3 million depressed adolescents in the USA who were supposedly at substantially increased risk of career failure, divorce, alcoholism or other substance misuse and suicide, all of which could, according to the *Newsweek* article, be averted by the new SSRIs just about to be approved<sup>240</sup>. There was no hint here that unhappiness in childhood might be different than adult depression. The thrust of the article was that a failure to treat with medication would be equivalent to failing to give an antibiotic to a child with a life-threatening infection.

When FDA approved Prozac, Paxil and Zoloft for use in adults in the early 1990s, they noted that the drugs were likely to be used to treat children, and encouraged companies to run studies to establish the safety of the drugs in children. Sales of SSRIs for children had been creeping up steadily through the 1990s on the back of over 70 published “open studies” of these medicines – all claiming the drugs were marvelous. Open studies are ones in which a doctor knows what the drug is and the patient may be told as well. They invariably report positive results for a drug, but companies cannot use this kind of study to get marketing approval from FDA; they can only use randomized studies.

Because there were so few good studies for any drugs in children, in 1998 an FDA Modernization Act (FDAMA) offered pharmaceutical companies a six-month patent extension for a drug if they submitted studies that examined safety issues in children. They didn’t have to prove safety. They just had to test for it. If the drugs showed hazards, the company still received the patent extension but would have to incorporate

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<sup>240</sup> *Newsweek*, *Depression: 3 million Kids Suffer From It. What You Can Do*, pp 52-61, October 7th 2002 .

the hazard information in the label<sup>241</sup>. This offer of patent extension gave the companies a hefty incentive to submit studies to FDA on the effect of their drugs on children. A six-month patent extension for a Paxil or Zoloft meant easily over \$1 billion in additional revenues. And there was every chance that FDA would miss the problems.

As a result, in 2003 when NICE set about drawing up a guideline on the treatment of childhood depression six randomized trials of SSRIs in children had been published<sup>242</sup>. The new guidelines were set to endorse the use of Prozac and other SSRIs for children<sup>243</sup>. The use of these drugs was increasing rapidly in Europe and this endorsement would likely have opened a floodgate.

In the case of Prozac there were two Lilly trials. Graham Emslie from Texas, who had participated in drawing up the TMAP guidelines for children, was involved in both. In clinical trials, it is customary to specify a primary measure of the success of treatment – such as the score on a particular rating scale or blood test--and if the drug fails to beat placebo on this measure, the trial is considered negative. On this basis, the first Emslie study, which started in 1990 but was only published in 1998, was a negative study even though the published article claimed it was a positive study<sup>244</sup>.

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241 Vera H.Sharav, *The impact of FDA modernization Act on the recruitment of children for research*, Ethical Human Sciences and Services 5, 83-108 (2003).

242 Martin D.Keller et al., *Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial*, Journal of the American Academy for Child and Adolescent Psychiatry 40, 762-772 (2001).

243 Tim Kendall, Linsey McGoey and Emily Jackson, *If NICE was in the USA*, Lancet DOI:10.10116/5c E (2009).

244 Graham J. Emslie et al., *A double-blind, randomized placebo controlled trial of fluoxetine in depressed children and adolescents*, Archives of General Psychiatry 54, 1031-1037 (1997). The internal FDA medical review of the trial makes it clear it was a negative study.

A second study, published in 2002 was also negative. In this, after the first week of the study, all children who had a bad reaction to Prozac or a good response to placebo were excluded<sup>245</sup>. It is common for a company to load the dice in its favor by excluding anyone who responds to placebo in the initial phase of the trial, but it was almost unheard of at the time to take the extra step and exclude patients who reacted poorly to the experimental drug during the first week of their exposure to it. If they dropped out of the study, they should be counted as drop-outs for adverse events, not eliminated from the study calculations entirely. This novel tactic has since been increasingly copied in company trials of drugs for asthma, hypertension and other conditions.

In the case of Paxil, the key study and the largest of the SSRI trials was 329, which as we have outlined in chapter 4 was a negative study that Sally Laden of Scientific Therapeutics Information transformed into an article demonstrating the remarkable efficacy and safety of Paxil. In addition to 329, study 377 had also been undertaken in the 1990s but remained unpublished. Two further studies were presented at academic meetings in 2002, in which the claim was that Paxil was safe and effective<sup>246</sup>.

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245 Graham J. Emslie et al., *Fluoxetine for acute treatment in children and adolescents: a placebo-controlled randomized clinical trial*, *Journal of the American Academy of Child and Adolescent Psychiatry* 41, 1205-1215 (2002). . It is common in clinical trials to stop previous treatments and to put everyone on placebo for a week or two before starting the trial proper. This is called either the washout or the placebo run-in period, and its stated purpose is to washout any prior drug treatments. It is common to exclude patients responding to placebo during this period.

246 David J. Carpenter et al., *Safety of Paroxetine in the Treatment of Children and Adolescents with OCD*. Presented at the 40th annual NCDEU meeting, abstract 58 (2001) ; Daniel A. Geller et al., *Efficacy and Safety of Paroxetine in Pediatric OCD: Results of a Double-Blind Placebo Controlled Trial*. Presented at the 42nd Annual NCDEU Meeting, Session III-16 (2002). (Also presented at the APA annual meeting, Philadelphia, May 2002, NR 349); Karen D. Wagner et al., *Safety and Tolerability of Paroxetine in Children and Adolescents: Pooled Results from Four Multi-center Placebo Controlled Trials*. Presented at the 42nd Annual NCDEU Meeting, Session II-61 (2002).

The third of the major SSRI's was Zoloft. The FDA requires two controlled studies to let a drug on the market. Pfizer ran two studies. In each Zoloft failed to beat placebo<sup>247</sup>.

Just like 329, these studies were ghostwritten. In this case they were published in JAMA and in the process transformed into one positive study - Zoloft was deemed effective and well-tolerated. The design of these trials did not encourage the detection of any problems resulting from Zoloft, but even so, compared to children on placebo, there was a doubling of the rate of behavioral problems, including suicidality and aggression, in children on Zoloft and a tripling of the drop-out rate for side effects<sup>248</sup>.

By 2003, then, there was a series of articles all claiming the SSRIs worked, and so an impending endorsement by NICE did not seem surprising. GlaxoSmithKline had applied to the British regulator (the Medicine and Healthcare Products Regulatory Agency, MHRA) for a license to market Paxil for childhood depression. But in October 2002 and Spring of 2003 two BBC investigative journalism programs had questioned the benefits of Paxil<sup>249</sup>. Astonishingly, MHRA turned down GSK's application to license Paxil, and in support of their move took the unprecedented step of posting on its website the details of 15 controlled trials on antidepressants undertaken by a number of companies in pursuit of a license for treating pediatric depression. Depending on the way one reads the studies, between 12 and 14 of these 15 studies suggested the drug being tested didn't work and overall the studies showed a doubling of suicidal acts on the drugs compared to placebo.

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247 Karen D.Wagner et al., *Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials*, JAMA 290, 1033-1041(2003).

248 Karen D.Wagner et al., *Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials*, JAMA 290 1033-1041(2003).

249 Central Medical Affairs Team *Seroxat. Adolescent Depression. Position Piece on the Phase 111 studies*. October 1998. SmithKline Beecham Confidential Document, available from the author. This is also available on the Canadian Medical Association Journal Website.

It was clear from these posted studies that there were yet further data that GlaxoSmithKline had not sent to the regulator<sup>250</sup>.

NICE was faced with two problems. First, they worked from the published data but the MHRA posting made it clear there were many more studies. Of the at least fifteen studies conducted, only six had been published. The unpublished studies were all negative. The second problem was that even the published Paxil, Prozac and Zoloft studies, it was now clear, had been manipulated so that essentially negative studies were transformed into positive studies, hiding the fact the drugs didn't work and masking the problems of treatment. These revelations led researchers from NICE to pen an award-winning editorial in the *Lancet* – *Depressing Research*<sup>251</sup>. This pointed to the impossible position any guidelines agency was in if companies withheld trials and distorted the data to the extent that had happened in the case of the pediatric antidepressant trials. It was left unsaid, but the position for doctors whose legitimate concerns about giving drugs like Paxil to children might conflict with the guidelines, had they been instituted, would have been even worse. The position for the children would of course have been worst of all.

For a brief moment, some of those in NICE who had gone through this crisis toyed with the idea of insisting that the status of any evidence that came from company trials be downgraded. Up to this point, the rules of “evidence based medicine” had been that the results of clinical trials trumped everything else. Now it had become clear that

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<sup>250</sup> This statement is based on my knowledge of what trials had been undertaken from scrutiny of company databases and FDA's published statements about the trials that had been submitted to them.

<sup>251</sup> Editorial, *Depressing research*, *Lancet* 363, 1335 (2004).

companies were selective in what trial data they released, and thus company data appeared to be worth a lot less than had previously been assumed<sup>252</sup>.

But NICE dropped the idea of downgrading company trials. Could they be sure that a rule made on the back of the issue of antidepressants for children would hold water when it came to, say, trials of antihypertensives or analgesics or drugs for osteoporosis? If company evidence were to be downgraded, to what rung in the ladder should it be relegated – above or below the opinions of experts? Just how worthless was company evidence? And having dragged pharmaceutical companies into trials by insisting upon their necessity in order to gain a license, was this really the time to give them a slap in the face? Far better, surely, to work to improve company trials.

There had, moreover, apparently been one positive outcome of the debacle. The Paxil data that MHRA made public confirmed the message of an internal GlaxoSmithKline memo that had come to light in the BBC investigations: that study 329 had shown Paxil was not effective, so only the good bits of the data would be published. At hearings the FDA held in February 2004 on prescribing antidepressants for children I made it public. It found its way from there to the offices of New York's Attorney General, who sued GlaxoSmithKline for fraud, and as part of the settlement, the company agreed to register all its trials on the web.

The idea of a clinical trial register took off. Journals indicated that they would in the future only publish accounts of trials that had been registered with a central trial register

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<sup>252</sup> This is based on conversations with the key players in NICE at this time.



beforehand and been given a unique identifier. Such an identifier would have made it easier to establish that only four trials underpinned the 243 publications on Zyprexa. But clinical trial registers and Glaxo's posting to its website do nothing to change the basic problem, which is companies still do not made the raw data from these trials available.

NICE finally did issue a guideline on pediatric depression in 2004: they recommended against using SSRIs as a treatment. In 2004, FDA held a further regulatory hearing in September to follow up the February hearing. These hearings on antidepressants and suicidality in children led to the highest level of warning, a black box warning, being put on the drugs indicating that they might trigger suicidality. FDA meanwhile did not license Paxil or Zoloft or other antidepressants for use in children.

Far from this being a case of all's well that ends well, however, the use of antidepressants in children shows how far our scientific standards have slipped and how this impinges on our ability to care for some of the most vulnerable people there are. These studies of antidepressants in children offer the greatest known divide in medicine between what published reports in the scientific literature say on the one side and what the raw data in fact show, but there is no reason to think this problem doesn't extend to other treatments in other areas, from drugs for osteoporosis to treatments for asthma, female sexual dysfunction, PTSD or other disorders. There was another landmark also – this was the only known case where all of the published studies were ghostwritten or company written.

The fifteen controlled studies of these new antidepressants should stand as a celebrated example of what controlled trials are there for – to stop bandwagons in their tracks. But instead, between ghostwriting and selective publication of the data, companies have turned controlled trials into their primary means to turbo-charge sales. The published papers endorsing the use of Paxil, Prozac and Zoloft remain published in the best journals and continue to fuel a boom in off-label sales of these drugs to children<sup>253</sup>. There have been efforts to get Study 329 retracted but these have failed<sup>254</sup>. It continues to be built into guidelines supporting the use of antidepressants for children.

Erick Turner formerly a reviewer with the FDA has demonstrated that a third of the studies undertaken to get current antidepressants on the market for adults remain unpublished but even more worryingly a third of those published were studies FDA regarded as negative but that like study 329 companies published as positive<sup>255</sup>.

In other areas of medicine, where the problem has not been forced out into the open, companies can use their published studies to capture guidelines as they had almost done

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253 Anyone involved in framing guidelines is now involved in business and their judgments can have far reaching financial consequences, as the money involved in the patent extensions for the SSRIs demonstrates. The story of another SSRI given to children may make this clear. Celexa (citalopram) was discovered by the Danish company Lundbeck and marketed by Forrest Laboratories in the United States. In 1996, Lundbeck started a trial of Celexa in children that wasn't published until 2006. In 2002, Forrest ran another study of Celexa in children in the United States. As the controversy surrounding antidepressants for children grew, Forrest personnel made presentations of their "data" for Celexa which appeared to show it worked and was free of risks. A ghostwritten report on the results of the second study was published in June 2004 (Karen D. Wagner et al., *A randomized placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents*. American Journal of Psychiatry 161, 1079-1083 (2004)). There was no mention in all this of the earlier, unpublished Lundbeck study in which Celexa had failed to beat placebo and in which the rate of suicidality on Celexa was dramatically higher than on placebo (A.L. Von Knorring et al., *A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder*, Journal of Clinical Psychopharmacology 26, 311-315 (2006)). To the stock market analysts reviewing company share prices, Celexa looked good compared to the other drugs, which were running into trouble at the time. The Teamsters Union invested pension funds in the stock, while company board members sold stock and made money. As news of the earlier study spread, however, the value of Forrest's stock dropped. The Teamsters Union then took a securities action that resulted in a \$65 million judgment in their favor (B. Maier and B. Carey, *Drug maker accused of fraud*, New York Times Feb 25th 2009. [http://www.nytimes.com/2009/02/26/business/26drug.html?\\_r=3&ref=health](http://www.nytimes.com/2009/02/26/business/26drug.html?_r=3&ref=health)). There is clearly a lot more at stake in these exercises than there ever had been in traditional medical trials.

254 Melanie Newman, *The rules of retraction*, BMJ 341, 1246-1248, c6985 (2010).

255 Erick H. Turner et al., *Selective publication of antidepressant trials and its influence on apparent efficacy*, New England Journal of Medicine 358, 252-260 (2008).

in the case of antidepressants given to children and, as we shall see, they continue to do in other domains. But even when the guideline is not captured, such studies and their publications transform the way we view things. In the case of antidepressants and children, for example, there is no longer any appreciation that childhood unhappiness might be anything different from adult depression. Someone attempting to express such a view today would find it difficult to get acceptance in anything other than a marginal journal.

### **THE CAPTURE of THE BIPOLAR GUIDELINES**

Classic manic-depressive illness, which typically leads to periods of hospitalization, was and still is rare. The recent invention of Bipolar disorder obscures this but reveals much about how companies capture guidelines. When patients with the classic illness were admitted to hospital, either manic or depressed, they were typically too ill to recruit to a controlled trial. This is not as problematic for good clinical care, including care that involves pharmaceuticals, as it may sound, however. Clinical trials rarely lead to discovery of any new drugs. Chlorpromazine, for instance, the first of the antipsychotics, was discovered in the early 1950s in Paris as a treatment for mania – but not in the course of a clinical trial<sup>256</sup>. For the ensuing 40 years most doctors in America and Europe regarded both chlorpromazine and later antipsychotics as the mainstay of treatment for mania. No one in medicine saw a need to conduct a trial for something as obviously beneficial as giving these antipsychotics to manic patients.

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256 Jean Delay and Pierre Deniker, *38 Cas de psychoses traitées par la cure prolongée et continue de 4560 RP*, C.R.Congrès Méd Alién Neurol France 50, 497-502 P (1952).

That there had been no randomized trial data for these older drugs for mania opened up a golden opportunity for pharmaceutical companies to push these older drugs out of the market, when in the 1990s the companies came out with a series of new, albeit, as it turned out, no more effective and actually more hazardous antipsychotics. The way forward led through treatment guidelines.

Here's how it happened in the case of Bipolar disorder. The first step was to run short-term trials involving patients with much less severe conditions, and less certain diagnoses, using rating scales that may have reflected little more than how highly sedating were the drugs being tested. A strong sedative will always produce a "signal" on a rating scale for mania – the patient will be less active, less talkative, less disinhibited while under the influence of the drug. This is all it takes to get FDA approval for company claims their drug is anti-manic. As a result of these trials all guidelines from the first formulated by TMAP in 1998 to a set of NICE guidelines in 2006 recommend the use of on-patent antipsychotics – but not any of the older antipsychotics<sup>257</sup>.

The second step was to run debatably ethical trials elsewhere, such as one Janssen ran in 2003 and 2004 on Risperdal for mania in India<sup>258</sup>. This trial became the subject of a BBC investigation into the ethics of studies for Western treatments outsourced to India. Did patients know they were involved in research? Did they consent to it? Did they know that once their participation was over they would be removed from drugs that might have been helping them? And it wasn't just ethics that was at issue. The correspondence in the

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257 National Institute for Health & Clinical Excellence (NICE), *Bipolar disorder: Clinical Guideline 38* (2006). Available on [www.nice.org.uk](http://www.nice.org.uk)

258 Sumant Khanna et al., *Risperidone in the treatment of acute mania: Double-blind, placebo-controlled study*. *British Journal of Psychiatry* 187, 229-234 (2005).

columns of the *British Journal of Psychiatry* on the validity of this study was more extensive than for any other study the journal has published<sup>259</sup>.

In this newly globalizing clinical trial world, everyone faces a future in which the bulk of the evidence that dictates clinical practice when it comes to the use of statins, antihypertensives, pain-killers, antibiotics, and practically everything else from mental health to respirology will come from settings that are very different from those in which the treatment will be given. There are likely to be many consequences for clinical practice, not least because both efficacy and side effects of different medicines may vary markedly in different ethnic groups.

As a result of the trials undertaken in India and elsewhere, only the new antipsychotics had randomized controlled trial support. The older agents hadn't. The straitjacket of current notions of evidence-based medicine, as applied by guideline bodies like TMAP or NICE, places published evidence from controlled trials above everything else – almost to the point of not using a parachute until a study is undertaken to indicate formally their usefulness. What's more, the marketing departments of companies depend on our fascination with this dynamic and use it to capture the process of developing guidelines.

The third step involves something close to checkmate. In the case of manic-depressive illness the only agent with an established prophylactic effect is lithium. But modern guidelines also variably recommend Zyprexa, Depakote and other new antipsychotics or anticonvulsants even though these are not licensed for this purpose. This has essentially

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259 Sandhya Srinivasan et al., *Trial of risperidone in India – concerns*. *British Journal of Psychiatry* 188, 489-492 (2006).

happened because Abbott heavily advertized Depakote as a mood-stabilizer in the first instance and the companies with follow-up anticonvulsants and antipsychotics followed suit. This term generates expectations of a prophylactic effect even though none has been shown. Claiming Depakote was prophylactic would have been illegal – but there was no need for Abbott or other companies to tempt the law when a prestigious guideline recommends Depakote for a use the regulator would not let you claim. In this case, bound by the law, FDA is a lot more stringent than the guideline makers. This is advertising that's hard to beat.

The final step involves the use of guidelines to create new disorders. Over a century of clinical opinion has unanimously held that bipolar disorder can occasionally start in adolescence but usually has an even later onset. The guidelines makers are trapped into mentioning pediatric bipolar disorder by the simple fact that companies have published a number of trials giving sedative drugs to unruly children, labeled as suffering from bipolar disorder. Being value neutral, because trials had been run, in their 2006 guideline NICE had to mention pediatric bipolar disorder. In so doing they breached a century of worldwide clinical consensus, and all but endorsed the disorder, pushing Europe down a route America has already traveled<sup>260</sup>.

When it comes to bipolar disorder, American medicine is in the grip of an enthusiasm reminiscent of the 17<sup>th</sup> century Dutch tulip mania. Children as young as one year of age are being put on antipsychotics, and some clinicians even contemplate the possibility of

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<sup>260</sup> There are 2 versions of the guideline. A longer technical version that makes it clear childhood bipolar disorder should not be diagnosed unless children meet the criteria for the adult form of the illness. And a shorter version that does not mention this. The shorter version is the one that has been disseminated.

making in utero diagnoses. Guidelines have been a significant factor in this infection. In recent years a series of pediatric bipolar consensus conferences were organized in the US, such as one organized by Best Practices, a marketing firm specializing in central nervous system drugs<sup>261</sup>. This conference was supported by all the major pharmaceutical companies, and its final recommendations were ghostwritten, but even if such meetings weren't financially supported in this way, with carefully sculpted ghostwritten recommendations the result would likely have been the same. Running trials of sedative drugs in overactive or disruptive children, who are labeled bipolar, will produce an apparent benefit. That clinical trial result in effect pulls a guideline into existence, and if there's a guideline, the condition is assumed to be real. All the marketing company need do is ensure the guideline making process happens in a timely fashion, with a consensus statement for publication and dissemination.

Once the participants agree that the guideline has to be based on clinical trial evidence, the guideline all but writes itself before the participants sit around the table. The guidelines produced by TMAP in 1998 for the treatment of Bipolar disorder are essentially indistinguishable from those produced by NICE in 2006. Where in 2004 NICE were saved by a television program from contributing to making children depressed, nothing saved them in 2006. The reasons for NICE's failure to distinguish itself from TMAP in 2006 do a great deal to help explain our current healthcare problems.

## **FACTS ON THE GROUND**

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<sup>261</sup> <http://www.best-practice.net> accessed Jan 4th 2010

Across medicine, however misleadingly certain academic papers may be written, with a few exceptions, no studies allow claims that one drug is superior to another. Even so, a series of guidelines in different areas of medicine advocate newer, more expensive drugs over older ones, as we've seen. However well-meaning these may be, there should in these cases be suspicions that the guideline has been captured by pharmaceutical companies.

Capture is engineered by a combination of smart publication strategies and targeting trials at illnesses where there have been no trials before, whether restless legs syndrome, female sexual dysfunction (FSD) or osteoporosis. In these ways, companies can make diseases fashionable, can engineer the appearances of comparative efficacy and can enlist academic advocates for particular treatment options. By these means, too, they have been able to control the content of guidelines and transform even independent guidelines into something close to an extension of company marketing departments.

This dynamic plays a key role in the selling of diseases from FSD, to PTSD, overactive bladder<sup>262</sup>, osteoporosis and osteopenia. Getting a drug licensed for FSD or osteoporosis does not mean that physicians are thereafter enabled to treat women in a more effective way than they had been able to do before. Rather, it means that Pfizer, Lilly and GlaxoSmithKline are enabled to start marketing these disorders and in the process to convert the vicissitudes of intimate life on the one hand or the changes of middle years on the other hand into illnesses. Guidelines achieve even more for a company – they make it

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<sup>262</sup> In the case of overactive bladder, in clinical trials patients on anticholinergic drugs like Detrusitol used in instances of what once was called urge incontinence go to the toilet one less time in 48 hours. Renaming the condition as overactive bladder increased the numbers of patients from 12 to 30 million in the US with trials showing the same minimal benefit – but substantial side effects.



appropriate, indeed almost necessary, to detect and treat these illnesses. Company sponsored and ghostwritten “scientific” papers, along with selectively presented trial results offer the raw material out of which clinical consensus will later be manufactured. When it comes to annexing territory, this clinical consensus in the form of guidelines establishes facts on the ground.

Consider what happens when a guideline is published. For managers running healthcare institutions, there need to be standards against which the organization can be held accountable. Whether or not the current guidelines are wrong is immaterial. If attempting to implement them produces no health gain, this still makes no difference to a manager, at least in his strictly institutional role. The key point is adherence.

A celebrated episode from the 4<sup>th</sup> series of the American medical drama *House* shows Dr Foreman grappling with a patient’s life-threatening problem. He ultimately finds an unorthodox answer to it that saves his patient’s life but gets him the sack. As his boss tells him, it may have been good Medicine but it was bad practice. Dr Foreman is not alone; clinicians worldwide are increasingly faced with managers enquiring about their compliance with guidelines and more and more are getting the sack. What’s a manager going to do if a doctor tells him that these ostensibly evidence-based guidelines amount to pharmaceutical marketing by proxy?

The accountants in the finance department of a healthcare organization who see the figures on newer and more costly drugs also find themselves faced with guidelines

supporting the use of these drugs, issued by independent academic bodies whose stated brief is, in part, to secure cost effectiveness. The promise is that the organization will save money in the longer run by being “evidence based,” as this will lead to better outcomes for diseases treated this way and to savings on not doing what works less well. The beans line up for both the accountants and executives. Truth does not.

Articles by guideline proponents, and even the guidelines themselves state that clinicians do not always need to adhere to the guidelines – this is guidance rather than a diktat<sup>263</sup>. But the medico-legal articles suggest that any deviation from guidelines needs to be justified. Where a clinician wouldn't have to justify guideline-sanctioned treatment in the medical record, they are advised to justify everything that is “unorthodox”. Doing anything different, then, adds to the bureaucracy, and increases the sense of risk.

An element of coercion has also emerged in many medical settings where reimbursement has been tied to guideline adherence. The element of coercion increases further if one considers that current evidence is framed within settings in which pharmaceutical companies advertise (in the US) and set up patient groups who lobby for new treatments even though there is no evidence to believe these are any better than older treatments.

The proponents of guidelines put them forward as guidance and believed that they could only lead to improvements in the outcomes of treatment for all conditions. But a series of studies have shown that the outcomes, on average, are in general no different whether or

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263 P. Colbrook, *Can you ignore guidelines?* BMJ Careers, 143-144 (9th April 2005).

not clinicians adhere to guidelines<sup>264</sup>. Soon after guidelines began to appear in the 1980s, opposition to them emerged and grew steadily.

Clinical concerns that guidelines risk becoming coercive are often met with a cynical response - of course clinicians will be worried if their autonomy is being curtailed. While not untrue, this misses an essential point: If a treatment really works, both because they want to help their patients but also for reasons of compelling self-interest few clinicians are likely to fail to prescribe it whatever the guidelines may say. Who would not give penicillin to a patient with pneumonia or an antipsychotic to a floridly manic patient?

The problem guidelines might pose was outlined first in 1956 long before anyone had heard of them. Following the discovery of the first antipsychotic, chlorpromazine, the National Academy of Science and National Institute of Mental Health (NIMH) convened a meeting to work out how to build on this discovery. Ed Evarts from the NIMH, one of the leading lights of the day, put it to his colleagues that but for an accident of history they could now be discussing the use of the new antipsychotics for the treatment of *dementia paralytica* (tertiary syphilis) rather than *dementia praecox* (schizophrenia). Tertiary syphilis had looked identical to schizophrenia and chlorpromazine would have produced a distinct benefit on this state because it controlled the hallucinations and delusions that went with the disorder, although likely at a cost of increasing mortality – but this increase in mortality would not have shown up in the short-term clinical trials that demonstrated a benefit.

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264 Tim Croudace et al., *Impact of the ICD-10 primary health care (PHC) diagnostic and management guidelines for mental disorders on detection and outcome in primary care: Cluster randomized controlled trial*. *British Journal of Psychiatry* 182, 20-30 (2003); Peter Tyrer, Michael King and J. Fluxman, *Treatment of common mental disorders in general practice: are current guidelines useless?* *British Journal of Psychiatry* 183, 78 (2003).

Evarts pointed out to his audience that none of the rating scales, clinical trial methods, or animal models that were then being put in place as the engines of progress that would move the new psychopharmacology field forward would have helped doctors to work out that penicillin rather than chlorpromazine or psychotherapy was the right answer to *dementia paralytica*. What made the difference was understanding that tertiary syphilis was a microbial infection. He predicted that the proposed scaffolding of clinical trials, although eminently sensible, would create an academic and industrial complex that would slowly stifle progress in therapeutics<sup>265</sup>.

No one paid heed to Evarts. He came to the conference as a leading figure within the psychiatry of his day but vanished from the radar afterwards – leaving a set of predictions that have been spot on the money. Fifty years later, compulsory detentions for mental illness have risen 3-fold, admissions for serious mental illness have risen 7-fold, admissions overall have risen 15-fold<sup>266</sup>, suicide rates in schizophrenia have gone up 20-fold<sup>267</sup>, and diseases such as diabetes have increased exponentially among the mentally ill<sup>268</sup>. There has been a dramatic drop in life expectancy for serious mental illness in America – with a fall of up to 2 decades compared with the rest of the population.<sup>269</sup>

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265 Edward Evarts, "A discussion of the relevance of effects of drugs on animal behavior to the possible effects of drugs on psychopathological processes in man". In *Psychopharmacology: Problems in Evaluation*, Jonathan O. Cole and Ralph W. Gerard (eds.) (Washington D.C.: National Academy of Sciences/National Research Council, 583, 284-306, especially page 302, 1959).

266 David Healy et al., *Psychiatric bed utilisation: 1896 and 1996 compared*, *Psychological Medicine* 31, 779-790 (2001).

267 David Healy et al., *Lifetime suicide rates in treated schizophrenia: 1875-1924 and 1994-1998 cohorts compared*, *British Journal of Psychiatry* 188, 223-228 (2006).

268 Joanna LeNoury et al., *The incidence and prevalence of diabetes in patients with serious mental illness in North West Wales: Two cohorts 1875-1924 and 1994-2006 compared*. *BMC Psychiatry* 8, 6 doi:10.1186/1471-244X-8-67 (2008).

269 Craig W. Colton and Ronald W. Manderscheid, *Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states*. *Preventing Chronic Disease*, Volume 3, Number 2 (2006). Available from: [http://www.cdc.gov/pcd/issues/2006/apr/05\\_0180.htm](http://www.cdc.gov/pcd/issues/2006/apr/05_0180.htm).

The same has been found wherever else these things have been measured<sup>270</sup>, with increases in mortality correlated with the numbers of psychotropic drugs given<sup>271</sup>.

We have focused on mental health in this chapter, but the same is happening in other areas of medicine where there are blockbuster drugs. The interaction between the first of the blockbusters, Zantac, and the treatment of ulcers, outlined in chapter 2, bears out Evarts' prediction better than anything else. Many doctors had been using antibiotics for ulcers before Barry Marshall demonstrated that ulcers were often caused by the *helicobacter pylori* bacillus. Had there been guidelines for the treatment of ulcers then, any doctors prescribing antibiotics would have been at greater risk of a lawsuit than they might have been before the guidelines was formulated.

Current cardiovascular guidelines all mandate lowering low-density lipoprotein (LDL). Company marketing took advantage of this with Merck and Schering Plough suggesting that Vytorin (a combination of ezetimibe and simvastatin) would lower LDL cholesterol further than would treatment with a statin alone. The thrust of the guideline played into the marketing of Vytorin – until the clinical trial evidence finally demonstrated that prescribing Vytorin produced no benefit in terms of mortality<sup>272</sup>. Hormone replacement therapy entered guidelines as a means of lowering cholesterol, but it is now clear this

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270 Urban Osby et al., *Time trends in schizophrenia mortality in Stockholm County, Sweden: a cohort study*. *BMJ* 321, 483-484 (2000).

271 Matti Joukamaa, Markku Heliovaara and Paul Knekt et al. *Schizophrenia, neuroleptic medication and mortality*, *British Journal of Psychiatry* 188, 122-127 (2006); David J. Osborn et al., *Relative risk of cardiovascular and cancer mortality in people with serious mental illness from the United Kingdom's General Practice Research Database*, *Archives of General Psychiatry* 64, 1123-1131 (2007); Suhanta Saha, David Chant and John McGrath, *A systematic review of mortality in schizophrenia*, *Archives of General Psychiatry* 64, 1123-1131 (2007).

272 J.J.P. Kastelein et al., *Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia*, *New England Journal of Medicine* 358,1431-1443 (2008); Pfizer's torcetrapib was billed as doing the same, while still in development, but this development was ultimately stopped owing to a greater mortality in patients given torcetrapib (P.J. Barter et al., *Effects of Torcetrapib in Patients at High Risk for Coronary Events*, *New England Journal of Medicine* 357, 2109-2122 (2007)).

increases death rates<sup>273</sup>. Cardiovascular guidelines also call for optimal control of blood pressure and company marketing has suggested adding angiotensin receptor antagonists (ARBs) to ACE inhibitors as one way to do this, but the clinical trial evidence now suggests that this also increases mortality<sup>274</sup>.

For the treatment of diabetes, guidelines recommend tight glucose control.

GlaxoSmithKline's Avandia (rosiglitazone) was promoted as doing just this, making the company billions of dollars annually in the process, until it was withdrawn following evidence that Avandia increases rates of heart attacks and death, by up to 500 cases per month above what might have been expected had other agents been used<sup>275</sup>. The question of whether GlaxoSmithKline knew about these risks and hid clinical trial data – just as they did with Paxil in both children and adults – became the subject of a US Senate investigation as we shall see in chapter 7<sup>276</sup>. More generally large-scale studies have shown that adhering to these diabetes guidelines have led to higher death rates and more hypoglycemic episodes than found in patients treated with less emphasis on tight glucose control without any compensatory benefits<sup>277</sup>.

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273 Writing Group for the Women's Health Initiative Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial*, JAMA 288, 321-333 (2002).

274 Ontarget, *Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events*, New England Journal of Medicine 358,1547-1559 (2008).

275 Steven E.Nissen and Kathy Wolski, *Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes*. New England Journal of Medicine 356, 2457-71 (2007).

276 Committee on Finance, United States Senate, *Staff Report on GlaxoSmithKline and the Diabetes Drug Avandia* (2010). <http://finance.senate.gov/press/Gpress/2010/prg022010a.pdf>

277 Craig J.Currie et al., *Survival as a function of HbA1c in people with type 2 diabetes:a retrospective cohort study*, Lancet DOI:10.1016/S0140-6736(09)61969-3 (2010); Advance Collaborative Group, *Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes*, New England Journal of Medicine 358, 2560-2572 (2008); Action to Control Cardiovascular Risk in Diabetes Study Group, *Effects of Intensive Glucose Lowering in Type 2 Diabetes*, New England Journal of Medicine 358, 2545-2559 (2008).

The country that consumes the greatest amount of on-patent medications and the greatest amount of medications attested to by the most authoritative guidelines is the United States, but over the past decade, American life expectancies have progressively fallen behind other developed countries<sup>278</sup>. Over the same period of time spending on health has escalated in the United States beyond elsewhere, rising from less than 1% before the Second World War per annum to over 17% of GDP now. This is not what happens when treatments work. It is not what happened to the clinics and beds used to treat patients with tertiary syphilis after the discovery of penicillin, or tuberculosis after the development of streptomycin - when the patients vanished, the beds were closed down, the staff redeployed, and money was saved. The promise of the guideline makers – that if only policymakers follow the evidence (such as it is), health will improve while costs come down – has not held up.

When faced with evidence that guideline-mandated treatment with statins, antidepressants or drugs for osteoporosis fails to make a difference, guideline makers sometimes attribute this failure to a delay in the institution of treatment. In July 2008 the American Association of Pediatricians issued a new guideline on the health of children. It recommended screening children as young as 8 years old for raised cholesterol levels, and the possible institution of treatment with a statin<sup>279</sup>. The promise is held out that catching people ever earlier will make a difference. Similarly, advocates of mood-stabilizers commonly attribute failure of their drugs to make a difference down to the

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278 Karen Davis et al., *Mirror, Mirror on the Wall: An international update on the comparative performance of American Health Care*, The Commonwealth Fund (2007).  
. [www.commonwealthfund.org/Content/Publications/Fund-Reports/2007/May](http://www.commonwealthfund.org/Content/Publications/Fund-Reports/2007/May); John Abramson, *Overdosed America* (New York: Harper Perennial, 2005)

279 [www.aap.org/advocacy/releases/july08lipidscreening.htm](http://www.aap.org/advocacy/releases/july08lipidscreening.htm), accessed December 15th 2009

delay in starting the drugs, and they suggest catching and treating ever and ever younger children. Once the disease takes hold it is supposedly more resistant to treatment.

It seems strikingly difficult for clinicians and others to ask whether robust independent assessment of drugs can be undertaken in a world where data is privately held. The reviewers for the NICE guidelines teetered on the brink of making this point but backed down. The point was finally made in January 2011 by the Cochrane Centre Reviewers of Tamiflu who made it clear that in the current circumstances we have little option but to recognize that independent assessment of drugs is not possible<sup>280</sup>. There has so far been a deafening silence from Western Governments, all of whom have handed over billions of dollars to stockpile a remedy little better than one of the proprietary nostrums from the 19<sup>th</sup> century.

Some years ago, there was consternation in the Lake District of Britain, an area known for its narrow country roads and stone walls, as a growing number of juggernaut haulage trucks came roaring off the motorways and down the narrow roads, knocking over walls, getting stuck in the middle of towns and sometimes damaging property. The drivers were on autopilot. Alerted by their satellite navigation systems to delays ahead and advised of alternate routes, they followed the guidance. Putting patients on every drug indicated by a guideline – guidelines drawn up for diseases rather than for people – demonstrates a comparable blindness. The consequence polypharmacy constitutes a disorder in its own right if not an illness. Getting people off their medications has been demonstrated to

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280 Thomas Jefferson, Peter Doshi, Matthew Thompson and Carl Heneghan, *Ensuring safe and effective drugs: who can do what it takes?*, BMJ 342, 148-151 (2011).



reduce hospitalizations, reduce costs and save lives.<sup>281</sup> But doctors adopting this approach are getting and will get the sack, unless they can appeal to a guideline for treating people rather than diseases.

Some of us put on a guideline-mandated treatment will know when the new treatment is causing us problems; at that point surprisingly few of us have the fortitude to insist on the treatment being changed or stopped. Children have an even more difficult problem.

Their complaints have to be filtered through a parent who is no more likely to think a doctor would do anything that might harm their child than once they might have thought a cleric capable of abuse. Children are even more likely to be hostages than Bill put on an ACE inhibitor after his stroke or Sheila put on a statin after her cardiac event, as the case of Aliah Gleeson, forcibly removed from her family and treated according to the latest guidelines, demonstrates.

Sheila, Bill, Aliah, and the rest of us, are increasingly faced with doctors who are treating diseases rather than treating us. There are no guidelines for treating us. There are only guidelines for the treatment of cholesterol levels, or diabetes or depression. These doctors are caught in the pincers of an apparatus which is now being used to give us diseases and indeed often several different diseases at the same time. This apparatus has twin pincers – one pincer lies in the guidelines, the other formed by a series of measurement technologies that now are being used to make us ill in ways we weren't before. It is to these measurement technologies and how they are used that we now turn.

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281 Doron. Garfinkel D, Sarah.Zur-Gil and Joshua Ben-Israel, *The war against Polypharmacy: A New Cost-Effective Geriatric-Palliative approach for improving drug therapy in disabled elderly people*, Israel Medical Association Journal 9,430-434 (2007); Doron.Garfinkel and Derelie Mangin, *Feasibility study of a systematic approach for discontinuation of multiple medications in older adults*, Archives of International Medicine 170, 1648-1654 (2010).