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Investigation

Death of the magic bullet

We have learnt to place our faith in pills. But at what cost? As more and more prescription drugs are withdrawn because of adverse side effects, new figures suggest that the medicines we take are killing up to 20,000 people a year in the UK — six times as many as die on Britain's roads. Rose Shepherd reports

Mark's death in March 2004 was horrific. He'd been feeling low and losing sleep, and his doctor had prescribed promazine, an antipsychotic, although Mark, 49, had no symptoms of psychosis — until he took the drug. After two tablets he started to act oddly, saying he felt he could control things with his mind. After a third tablet, James, his partner of six years, saw him stepping agitatedly from foot to foot as he talked strangely on the phone, and then he fell. "He said he was okay," recalls James, "but I went with him to the surgery and we saw a different GP, who took the tablets off us and said Mark should be all right."

That evening, as James tried to go into the kitchen, Mark blocked his way and scuffled with him in the hall. James pushed him out of the front door, and Mark, "the quietest person", lobbed a paving slab through the window.

"He calmed down, so I let him in, then phoned 999. The police and ambulance came and asked Mark if he was okay, and left us to it. When Mark had gone to bed, I phoned the duty doctor, who said some people react that way to medication. He didn't feel a need to come out. I fell asleep but was woken by Mark screaming. He had locked himself in the bedroom. I called and he came to the door. He was trying to say something, but the words weren't coming. Then he fell on his back, really screaming. It looked like he was having an electric shock." James was on the phone to the emergency services when the screaming stopped. He found Mark lying on the stairs. There was blood in his mouth. The paramedics arrived promptly, but too late.

James was summoned to the police station, not to talk about the drug that might have killed Mark, but to raise the possibility that he had. "The inquest seemed mainly about establishing it was an accident. They said they believed Mark died of postural asphyxia after falling downstairs. Promazine was mentioned, but they never went into what caused him to have a fit. It is just my opinion that the promazine killed him."

According to the mental-health charity Mind's booklet Making Sense of Antipsychotics, adverse drug reactions (ADRs) to these drugs can include restlessness, unease, rocking from foot to foot, muscle spasms, aggression and, rarely, potentially fatal neuroleptic malignant syndrome, characterised by "sweating or fever... rigidity or loss of

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movement, difficulty in speaking or swallowing, changes in consciousness from lethargy and confusion to stupor or coma". Who knows, then, if it was the promazine, or perhaps an interaction between the promazine and other medication Mark had had? But shouldn't the possibility have been countenanced? There is a system in place for logging suspected ADRs.

The fact is, if someone you know is suffering from ADRs, you and they may not know it, and it may not be immediately obvious to your GP or even to a hospital consultant.

Allopathic medicine is founded on the belief that drugs are, all in all, a good thing; but we are now in a society awash with medications, and we have ushered in a killer. In a report in July 2004, the department of pharmacology and therapeutics at Liverpool University suggested ADRs account for 5,700 deaths a year on admission to hospital. If adverse reactions after admission were added, this could suggest a total of 10,000 deaths, while deaths from ADRs among those not admitted to hospital could be as many again. To put this in perspective, 3,221 people were killed on Britain's roads in 2004, and six times as many were killed by a legally prescribed drug, according to this study's conservative reckoning.

It has always been accepted that medicines can have dangerous side effects — hence the so-called "risk-benefit" trade-off. Even drugs in long and common use can cause ill in a susceptible few. And, with an industry under economic pressure to produce new drugs, these are prescribed without knowledge of their long-term side effects. It may take years for unwanted consequences to be known. They could even show up a generation later, as was the case with the synthetic oestrogen DES (diethylstilbestrol), prescribed to prevent miscarriage from around 1950 until 1975 in the UK, when it was found to cause a rare form of vaginal cancer in one in 1,000 girls exposed to it in the womb.

Most of us take pills at times, and we need clear information as to possible side effects. Yet packet inserts are skimmed, small-print affairs, while in medical schools there is a paucity of teaching of clinical pharmacology and therapeutics. Much of doctors' knowledge comes from advertisements, sales reps' spiel, industry-sponsored seminars, and a medical press seeded with ghosted articles that emphasise the positive.

The need to monitor drugs more closely became evident after the thalidomide debacle in 1964. Here in Britain, Sir Derrick Dunlop, chairman of the new Committee on Safety of Drugs (CSD), circulated a letter to doctors asking them to report promptly "any untoward condition in any patient that might be the result of drug treatment". Thus began the yellow-card scheme, implemented by Bill Inman, formerly with the medical department of the pharmaceuticals division of ICI. Under this voluntary reporting scheme, doctors were to notify the committee of suspected ADRs.

The Medicines and Healthcare products Regulatory Agency (MHRA) now collects yellow cards — submitted by health-care professionals and coroners, and by pharmaceutical companies under statutory obligations — assisted by the Committee on Safety of Medicines (CSM) and the Medicines Commission within the Department of Health. It is funded entirely by the pharmaceutical industry, and how it goes about its business is not for us to know. The Medicines Act, 1968, prohibits the disclosure of any information "obtained by or furnished in pursuance of this act". Professor Inman demurred. "I believe," he has written, "that all information about the effects of drugs should be available to any bona fide research worker from the first moment that the first dose is taken by a human being."

In 1965, Inman took home nearly 1,000 yellow cards relating to ADRs among women on the contraceptive pill. He arranged and rearranged them on his living-room floor, sorting and resorting them according to age, time on the pill, and whether or not the patient had died, until it became "glaringly obvious" that certain preparations of the pill caused thrombosis. Inman spent hours performing analyses that, he noted, "I would now have completed in minutes on a home computer".

The MHRA, under the chairman Professor Sir Alasdair Breckenridge (formerly of Glaxo's scientific advisory committee), enters yellow-card reports onto its Adverse Drug Reactions On-Line Information Tracking (Adroit) database. Doctors, pharmacists and scientists within the Pharmacovigilance Group of the Post-Licensing Division use this information and other sources to assess causal links between drugs and reported reactions. But is the authority performing any more effectively than did Inman, grubbing around on his carpet 40 years ago?

Not to judge by a recent inquiry by the Commons health select committee into the influence of the pharmaceutical industry, which describes a "lack of effective discipline and regulation", a "pervasive and persistent" industry, a "failing system of pharmacovigilance" and an "extremely passive" process of drug surveillance. The MHRA is, says the inquiry report, "oblivious to the critical views of outsiders and unable to accept that it has any obvious shortcomings... [its] attitude to its public health responsibilities suggested some complacency and a lack of requisite competency".

Charles Medawar, the founder-director of Social Audit, an offshoot of Ralph Nader's Public Citizen network in the US, with the pharmacologist Dr Andrew Herxheimer, carried out "probably the only independent analysis of what yellow cards say", to see if, in the case of the antidepressant Seroxat (paroxetine), the scheme was set up adequately to respond to reports of side effects. They found that forms that might raise suspicions of "suicidality" were often classified under different headings, thus reducing their impact, leading Herxheimer to conclude the system was "chaotic and misconceived".

"Most yellow cards lacked important information," Medawar writes in his book *Medicines out of Control*. "Three in four said nothing about past medical history, one in four recorded the 'outcome' of the reported reaction as 'unknown'. There was no evidence of regulatory follow-up of any reports of suicidal behaviour and injury/poisoning. Descriptions and comments were often nonexistent and typically brief." For example: "Suicide by cutting his throat" (hospital). "Pt shot himself a few days after starting medication" (GP).

Medawar was way ahead of the MHRA in declaring that antidepressants such as Seroxat, known as selective serotonin reuptake inhibitors (SSRIs), were addictive. "In a paper published by the regulator in 1996," he told me, "they concluded that the risk of withdrawal symptoms was 'rare'. Then, overnight, on June 25, 2003, a small-print change was made to the data sheet for Seroxat, saying the incidence is actually 25%. For about 15 years, the regulator failed to spot a side effect affecting one in four users."

The Augean stables are now being mucked out. Under reforms outlined in November, CSM members will be barred from having any links with pharmaceutical companies. The MHRA is to set up a Commission on Safety and Efficacy of Medicines, to include more lay and patient members as well as medical experts. But the best efforts of the CSM/MHRA will be undermined if doctors fail to file yellow cards. It is estimated that reports are submitted in as few as 10% of suspected ADRs. So 20,000-odd cards filed each year suggests as many as 200,000 cases.

In his oral evidence to the Commons inquiry in December, Richard Horton, editor of The Lancet, said five-yearly reviews of every drug on the market, "looking at what the evidence is for and against, would clear out all the dross and give up-to-date evidence for prescribers".

In January the Association of the British Pharmaceutical Industry (ABPI) weighed in, with executives from GlaxoSmithKline (GSK) and AstraZeneca, calling on the government to do more to ensure that doctors report side effects from new drugs. Stuart Dallow, for GSK, told the committee the scheme ought to be re-examined. This was rich from a company that, last August, paid £1.4m to settle a lawsuit brought by New York state's attorney-general, Eliot Spitzer, who accused GSK of withholding negative clinical-trial data on Seroxat. But the industry had to try to restore confidence in its blockbuster medications, amid continuing drug catastrophes.

In November, following the withdrawal of Merck's painkiller Vioxx, suspected of causing heart disease and strokes in tens of thousands, Dr David Graham, associate director of the US Food and Drug Administration (FDA), accused his agency of laxity in monitoring drug safety. The American public was "virtually defenceless", he asserted, if another medication proved to be unsafe after it was approved for sale.

The roll call of drugs withdrawn over four decades may be evidence of a system working — or a litany of failure. "Dross" medications represent a cost not only to the individual but to an ailing NHS. How high a cost? That's anybody's guess. While the Liverpool study was impeccable as far as it went, no under-16s were included, as one of the two hospitals surveyed had no paediatric unit. "We're planning to do a study at Alder Hey children's hospital," the research team leader, Professor Munir Pirmohamed, said. "Owing to lower drug usage in children, the overall scale of the problem is going to be smaller."

Yet minors are among the most vulnerable in society, and we are medicating them more and more. Prescriptions for mind-altering drugs rose from around 400,000 in 2000 to more than 700,000 in 2002. In the 12 months to June 2003, when the regulator warned that the benefits of the SSRI Seroxat in under-18s did not outweigh the attendant risk of suicide and self-harm, an estimated 8,000 young people had been prescribed the drug. Are so many children truly clinically depressed, or is this evidence of a reckless prescribing culture? Then children are, of course, targeted for vaccinations, and the 1979 Vaccine Damage Payments Act acknowledges that these can cause damage.

An estimated 25% of drugs given on general paediatric wards, and 65% of those given on neonatal intensive-care units, are licensed only for adults. Few clinical trials are conducted with children, not only because of ethical concerns, but because the market is too small to bear the expense. Thus, many medicines are given to children with limited guidance on dosage — although a new European regulation, expected to come into force in 2007, will provide both incentives and requirements for the industry to develop medicines for children where there is therapeutic need.

Reports of ADRs have not, traditionally, been accepted directly from patients, lest, presumably, they taint the rich scientific distillate. However, the MHRA is piloting reporting from patients and their carers. We have access to the agency via their website — and, perhaps more constructively, to communities of ADR sufferers via the internet.

ADRs may be physical, psychological, or both. Paradoxically, they may mimic the illness for which they are prescribed. We now know

SSRIs can cause depression, and that the risks of suicide, self-harm and violence are not unique to children. However, it is less well known that prescribed drugs, including antimalarials, antibiotics, antihistamines, steroids, painkillers, hormonal drugs and those for cardiovascular disease can have devastating psychiatric side effects.

Millie Kieve had no idea of this as, over years, she watched her daughter, Karen, suffer a series of ADRs to sulphasalazine, to the antipsychotics Haloperidol and Largactyl, to the hormonal drug Dianette, to dental anaesthesia, to Kemadrin (ironically, to treat ADRs) and the sleeping pill Temazepam. It was only after Karen, an ill, grey shadow of her former self, fell from a window of the family's Bournemouth flat that Millie realised the pernicious role played by medication. The day before she died, as she watched children playing on the beach, Karen had said to Millie: "Perhaps if things had been different, I might have had children of my own." There is something ineffably bleak about a woman aged 30 expressing such a sentiment, as though her life was over, as it so nearly was.

As the founder of April (Adverse Psychiatric Reactions Information Link), Millie spends her days researching, campaigning, assuring those suffering from ADRs that they are not "one in a million" freaks. "Listen, we need medicines," she stressed to me. Yes, but we also need to know that medicines can kill as well as cure. Consider Roaccutane (isotretinoin), a very powerful medication licensed for use for severe cystic acne. It was not appropriate for Jon Medland, who had just a few spots on his back. A 22-year-old medical student with brilliant prospects, Jon started on the drug on December 12, 2003. He returned home for Christmas, cheerful despite the dry lips and aches and pains that are expected side effects. A few days into January he rang to say he was having trouble sleeping, that he felt cold, and in a study session his mind had gone blank. Later he admitted he felt depressed. On January 8 he stopped taking the drug, but the depression deepened. He said he'd had "silly thoughts" about self-harm.

Over the next two or three days, Jon reported feeling better. Then, on the fourth day, one of his housemates phoned with terrible news. Jon's mother, Pamela, will never forget her husband, Jon, "yelping" with grief and distress before he turned to her to say their son was dead — hanged from a wardrobe by his belt. His farewell note said simply: "Sorry and goodbye".

The Medlands have no doubt Roaccutane was to blame. Sceptics say that it is acne, not a drug, that drives kids to suicide (as Roaccutane's maker, Roche, has suggested).

But Roaccutane has form. In its bulletin *Current Problems in Pharmacovigilance* (vol 24, August 1998), the CSM warned doctors to take precautions when prescribing the drug, "owing to serious adverse reactions". Product information was amended to strengthen cautions about depression and suicide. The warnings, writ large for years, finally made it into small print. Four years later, in this publication, Richard Girling documented a pattern of suicides, surely too numerous, too out of character, to be explained by depression over a skin condition.

At Jon Medland's inquest, the Manchester coroner Leonard Gorodkin, giving a verdict of suicide, stopped short of saying that Jon took his life "as a result of suicidal ideation brought on by Roaccutane". However, he noted: "For a drug to affect a person of very solid life foundation, if it can lead them to take their own life, it deserves further investigation. I cannot say with any certainty that the effects of the drug Roaccutane led him to take his own life. All I can say is that the warnings that are already present should be made very clearly and

strongly."

In a letter shown to me by a worried mother, dated March 25, 2003, R A Marsden, the president of the British Association of Dermatologists (BAD), stated: "Our association is becoming increasingly concerned by the reports of long-term side effects of Roaccutane, and we are considering commissioning a survey of our members." So why the scant, anodyne advice on the drug given in BAD's acne information leaflet, posted on its website? "Patients develop considerable drying of their lips and skin (especially of the face); some have mild aches and pains of their joints, and headaches. However, all these side effects can be easily and well controlled, such as by using a simple analgesic, like paracetamol."

The true tally of ADRs is, of course, unknowable, but one thing is certain: the more drugs we take, the more there will be, and the pharmas' remorseless emphasis on sickness militates against wellbeing.

In its evidence to the Commons inquiry, the Royal College of General Practitioners (RCGP) charged the drug companies with "disease mongering" by overstating the dangers of such conditions as hypertension, raised cholesterol, osteoporosis, anxiety and depression.

Marcia Angell MD was editor-in-chief of the New England Journal of Medicine. In her furious polemic, *The Truth about the Drug Companies: How They Deceive Us and What to Do about It*, she says that "Big Pharma" spends far more on promoting its products and courting prescribers than on research and development, and rather than discovering new drugs, it creates new diseases for existing ones. For "gastro-oesophageal reflux disease", read "heartburn". For "social anxiety disorder", read "shyness".

Drugs are not licensed until they have been tested, first on animals (an issue that divides scientists), then in three phases of clinical trials. Phase I experiments typically involve healthy volunteers, to study how a drug is metabolised and excreted, and to establish dosages. Phase II involves a small number of patients with the disease a drug aims to treat, with their informed consent. If all goes well, a full-scale Phase III clinical trial will involve perhaps 1,000 to 3,000 patients — too few to pick up on problems that may occur in perhaps one person in 100,000. The results of the phases are presented to the Medicines Control Agency and the CSM before the drug is granted a licence. Trials may run for just a few weeks, with no requirement to follow up the participants after withdrawal.

While the pharmaceutical companies' critics accuse them of skewing trials, their apologists hail them as the "gold standard". The metaphor is apt: it is about money. If you want to know what's driving modern medicine, skip the health section and turn to the business pages.

Clinical trials are unlikely to identify ADRs occurring in the long term, or in 1 in 100,000, hence post-marketing studies — and even here is a scam. Professor Inman writes: "Under the guise of 'post-marketing surveillance', some doctors are fooled into believing they are taking part in research and are paid to prescribe new drugs on ordinary NHS prescription forms. The patients are not volunteers and no explanation for change of treatment may be given. This prostitution of prescribing practice has been largely unchallenged by successive governments because of financial and employment consequences to the industry."

That the regulator is so slow to respond to warning signs adds insult to possible injury. As long ago as 1999, even as Vioxx was being

nodded through by the FDA, Dr Joseph Mercola was warning subscribers to his website: "You will see much in the media about this new brand of drugs, COX-2 inhibitors. However, taking these new drugs might be a matter of exchanging a gastrointestinal risk from one painkiller to a cardiovascular risk from another. Though the cardiovascular risk may be much more significant, I would strongly advise against using these drugs." This advice was based on a report in the Proceedings of the National Academy of Science. So the FDA knew there were dangers. Why wasn't it watching like a hawk?

Further warnings that their drug carried cardiovascular risk were sounded in March and May 2000, but it took more than five years for Vioxx to be withdrawn.

But don't let's be beastly to the pharmas. What else can they do? It is not so much that we need drugs as that drugs need us. Even were they able to find cheap, ingenious cures for all ills, they couldn't afford to do so. Entire corporations are drug-dependent. Most of their "innovations" are just reinventions. When a drug comes off patent, they tweak a molecule and produce a "me-too", which may be no better than the old. As Dr Ike Ihenacho, editor of the Drugs and Therapeutics Bulletin, told the Commons health committee, "If you look at all the drugs that are licensed in a particular year and critically assess whether these actually constitute genuine innovations for patients, you could be surprised, I think, to find that relatively few of them do."

In January the ABPI made a number of proposals to the health committee, including the recommendation that details of industry-sponsored trials be publicly registered, that summary results of such trials be published, and that all trials involving the NHS should include a requirement to publish as part of the contract. Leading companies have promised voluntarily to publish, on an internet database, results of trials sponsored by the industry.

How we got onto the treadmill of risky but officially sanctioned medicines is a difficult story. Many suggest that, in the drift from folk cures to scientific medicine, doctors lost touch with their patients, patients lost touch with their communities, and everyone forgot that staying healthy should be a life exercise, not a supermarket visit for pharmaceutical consumers.

Dr Benjamin Rush, physician to George Washington and a signatory of the Declaration of Independence in 1776, warned: "Unless we put medical freedom into the Constitution, the time will come when medicine will organise into an undercover dictatorship. To restrict the art of healing to one class of man and deny privileges to others will constitute the Bastille of medical science." Welcome to the Bastille.

OFF THE SHELF: DRUGS WITHDRAWN

In December 2003, Allen Roses, worldwide vice-president of genetics at UK GlaxoSmithKline, stated that more than 90% of drugs work in only 30 to 50% of patients. In September 2003 it was revealed that 14 drugs had been withdrawn in the past five years because of poor safety records. These included the blood-pressure medication Posicor, the diet pill fenfluramine, the tranquilliser Droperidol, and the heartburn drug Propulsid (cisapride). Other drugs banned since 1997 and suspected of causing deaths or serious side effects include the antibiotics Raxar and Trovan, the diabetes drug troglitazone, the anti-Parkinson's drug Tasmar, and the anti-cholesterol drug Lipobay (a statin). "All statins," commented the regulator, "have been associated with a risk of muscle disorders." Last August, statins were made available over the counter.

More recently, the Vioxx and co-praxamol painkillers have been pulled, as has the arthritis drug Bextra (valdecoxib), a COX-2 inhibitor. "The evidence suggests," noted the regulator, "an increased risk of thrombotic events associated with the selective COX-2 inhibitor class of drug."

Confusingly, banned drugs will often be given a reprieve and reappear on the market, licensed for the same or different purposes. Even thalidomide, the ultimate disaster drug, is in cautious use again for leprosy and some cancers.

WORRIED? DON'T PANIC

It can be dangerous to stop taking medications suddenly. Tell your doctor about any other drugs you are taking, and about your intake of alcohol, tobacco and caffeine. Cranberry juice can interact dangerously with warfarin; grapefruit juice with statins. If you suspect ADRs, ask your prescriber to submit a yellow card — or submit your own. Useful contacts: www.worstpills.org for information from Public Citizen; www.socialaudit.org.uk; www.april.org.uk; www.yellowcard.gov.uk for a patient reporting form.

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