Medical roulette: Dicing with death

29 July 2006 by **Hazel Muir**
Magazine issue 2562. **Subscribe** and get 4 free issues.

IT SEEMS like a foregone conclusion. People with mild symptoms of irregular heartbeat have a higher risk of sudden death. So give them drugs proven to help treat arrhythmia and you'll save lives.

This was just what doctors did in the 1980s. There was one problem: the drugs had been tested on and approved for people with severe arrhythmias. When clinical trials were eventually carried out in people with mild arrhythmias, they showed that, contrary to all expectations, the drugs doubled or tripled the risk of death.

> Doctors were convinced they were saving lives. But the drugs doubled the risk of death. They killed 50,000 people

"We were just shocked by what we saw," says pharmacologist Raymond Woosley, now at the University of Arizona in Tucson, whose team did the trials. "It took a long time for people to stop prescribing these drugs because they just couldn't believe it." It was later concluded that the heart drugs had killed 50,000 people. "That is a huge number. It was amazing to me that there wasn't more hue and cry."

This is an example of what can happen when drugs are prescribed "off label", meaning that they are used in a way not approved by regulators. Two decades on from the heart-drug scandal, you might think that it would be impossible for the same thing to happen again. Far from it. A report published earlier this year concluded that a fifth of prescriptions in the US are for drugs that have not been approved for the condition from which the patient is suffering. More importantly, for three-quarters of these prescriptions there is little if any scientific rationale. "What we've found over and over is that you cannot just assume the benefit will be there," says Woosley.

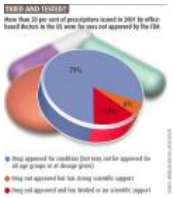
Prescribing drugs off-label is sometimes described as a form of human experimentation. But while a proper medical experiment involves volunteers and careful recording of results, doctors do not have to tell you that your prescription is off-label, and no one bothers to track who benefits and who suffers. Drugs can be used in non-approved ways for many years without anyone checking the outcomes.

This means people are probably still being killed by off-label prescriptions. "I can almost guarantee it," Woosley says. "All drugs can cause harm." So why do doctors persist in using drugs in ways for which there is little or no evidence? And what can be done about it?

The agencies that regulate drugs, such as the US Food and Drug Administration (FDA) or the UK's Medicines and Healthcare Products Regulatory Agency, demand that drug companies conduct rigorous clinical trials to prove a drug's safety and effectiveness in treating a particular disease. Then they approve the drug and its label, describing how the drug should be given, to whom and at what dosage. But these guidelines are not binding. Doctors can, with a few exceptions, prescribe drugs any way they want.

In many cases they have little choice. The most common form of off-label usage is to give drugs to people in groups on which it has not been tested, such as pregnant women, babies and children. Drug companies are naturally reluctant to run trials involving such people. Surveys of children's wards in hospitals across Europe suggest that nearly half of all drug prescriptions are off-label.

Depriving patients



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With this kind of off-label prescription, there is usually little doubt that a drug will help treat the condition for which it is given: the main issues are safety and dosage. Things become less clear, though, when a drug approved for one condition is used to treat another. This form of off-label prescribing is a natural last resort when seriously ill patients do not respond to standard treatments, or for rare diseases for which there is no approved treatment at all.

Yet off-label usage is not restricted to these extreme situations. Non-approved drugs are used to treat many common conditions for which approved treatments are available. Doctors argue this is justified because the pace of medical discovery is faster than the regulatory machinery: if an off-label treatment is the best option, surely it would be wrong to deprive patients of it just because the regulator hasn't rubber-stamped it yet?

"We have a policy, and it's enshrined in US law, that we don't want to let the government dictate to doctors how they should practise medicine," says Maxwell Mehlman, an expert on medical law at Case Western Reserve University in Cleveland, Ohio. "The FDA can say whether a drug is safe or effective, but it can't tell doctors what to use it for."

Indeed, in countries where doctors will not use a drug until it gets the green light from a regulator like the FDA, many people who desperately need a drug do not get it. Andrew Weeks, an obstetrician at the University of Liverpool, UK, highlights the case of misoprostol, a type of prostaglandin. When the FDA approved misoprostol to prevent stomach ulcers in 1988, obstetricians were intrigued, as prostaglandins are usually used to induce labour in pregnant women and prevent haemorrhage after birth. "In the Third World, the biggest maternal killer is haemorrhage following delivery," says Weeks.

Unlike other prostaglandins, misoprostol is very cheap, can be taken orally and does not need to be kept in a fridge. It seemed the ideal drug for women in developing countries. But misoprostol was a political hot potato in the US, because it can be used for abortion. Searle, the company that introduced the drug, did not want FDA approval for reproductive uses, so this research had to be publicly funded and was grindingly slow. The safe doses for inducing labour have only recently been established. Yet if doctors around the world did not use misoprostol off-label, many women would suffer as a result.

> If a drug has not been approved for treating a condition, how do doctors know it works? In most cases they don't

So there are good reasons for off-label prescriptions. Yet until a drug has been approved for a particular group of people or for treating a particular condition, how do doctors know whether it works, whether it is safe and what dosage to use? How do they know if it will turn out to save lives like misoprostol or harm them like the arrhythmia drugs? The answer is that in most cases they don't. The scientific basis for many off-label treatments is flaky at best, says Randall Stafford, an epidemiologist at Stanford University in California.

In May, he and his colleagues published their analysis of data from the National Disease and Therapeutic Index, an ongoing survey of office-based doctors in the US. In 2001, the survey sampled over 400,000 prescriptions given to patients. Stafford's team looked at patterns of prescribing for the 100 most commonly used drugs, as well as 60 others randomly chosen. They found that a fifth of prescriptions were for a condition for which the drugs were not approved by the FDA.

Then the team looked at whether these off-label uses had scientific support, in the sense of having been proven to be effective in controlled clinical trials or at least fairly large observational studies. The team found that three-quarters of the off-label prescriptions had little or no scientific support (*Archives of Internal Medicine*, vol 166, p 1021).

Top of the list was gabapentin (Neurontin), approved by the FDA for the treatment of epileptic seizures and pain from shingles. Yet 83 per cent of gabapentin prescriptions were for other conditions. For some of these off-label uses, such as easing social phobia and preventing migraines, there was scientific support. But two-thirds of all gabapentin prescriptions were for diseases that it might not be effective for, including bipolar disorder, depression and back pain.

Illegal marketing

Another example was risperidone, which at the time was approved only for treating schizophrenia. Stafford found that two-thirds of the prescriptions were for other conditions, none of which had scientific support. Doctors commonly prescribed risperidone for dementia, despite no clear proof that it works.

"Dementia is one of those situations where we don't have very good therapy, and there is a lot of patient and family demand for some sort of treatment," says Stafford. "But for a drug to be used in a few hundred thousand patients without

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adequate evidence, I think that's worrying."

Off-label treatment is thought to be higher in the US than other countries. General practitioners in the UK, for instance, are restricted by tighter budgets, says James McLay, a clinical pharmacologist at the University of Aberdeen, UK. However, no one has yet measured the extent of off-label prescribing among adults in the UK.

So why do doctors prescribe drugs off-label without good cause? Often, it just seems logical. It made sense that misoprostol would have similar effects to other prostaglandins, and this proved to be the case. But it also made sense that arrhythmia drugs would help in mild cases, and that turned out to be disastrously wrong.

The kind of "function creep" seen in the case of the arrhythmia drugs is common. Doctors tend to assume that if a drug works for one form of a condition, it will work for another. Almost all clinical trials of drugs for treating manic depression, for instance, have involved patients with the most severe form of the disease, called bipolar I. Now many such drugs are being dished out to people with milder forms (*New Scientist*, 15 April, p 38).

Stafford says there is also a tendency among patients and doctors alike to try out new drugs on the grounds that "newer is better". This is troublesome, he says, because newer is not necessarily better, but it is usually more expensive. Sometimes doctors might be persuaded of a drug's usefulness by early results presented at conferences, which may or may not be confirmed by later trials. And sometimes they are persuaded by the marketing tactics of drug companies.

The FDA forbids companies promoting off-label uses of drugs directly to patients, but they can promote such uses to doctors with certain provisos. The companies sometimes break the rules, though. In 2004, drugs giant Pfizer pleaded guilty to criminal charges because its Warner-Lambert division illegally promoted gabapentin for a host of off-label conditions. Company sales reps had paid doctors to give talks about off-label uses of gabapentin and to put their names to ghost-written articles singing its praises. The doctors received generous "consulting" fees as well as expenses-paid jollies to the 1996 summer Olympics. Pfizer was eventually forced to pay $430 million in penalties. "That is the most dramatic case that I'm aware of, but there have been a few others," says Mehlman.

In Stafford's study, gabapentin turned out to have the highest off-label prescription rate for any single drug. There is no proof that the illegal marketing was behind that, but Stafford says it certainly suggests that the influence of illegal off-label marketing deserves further investigation.

Death of the industry

So what should be done to prevent a repetition of the arrhythmia scandal? Everyone agrees that simply stopping off-label prescribing is not the answer. "If we were to ban unapproved uses, or restrict them to very formal research contexts, lots of people would not get treatments they need," says Mehlman.

Weeks thinks clear guidance from agencies like the UK National Institute for Health and Clinical Excellence (NICE) is the key. NICE's role is to make recommendations based on reviews of all the existing evidence. "If NICE recommends how to use a drug, everyone uses it and nobody actually cares whether it's off-label," he says.

Mehlman and Stafford would like to see an automated warning system that would be triggered when a doctor logs an off-label prescription. The system could suggest approved alternatives, and if the doctor persisted with their initial prescription it could store information about their reasons for doing so. That would both reduce off-label prescriptions and also create a clearer picture of off-label usage.

This summer, a pilot system along these lines will be tested in Scotland. McLay is leading tests of the software, which will alert doctors in six surgeries if they prescribe a medicine to children off-label. If successful, the software will be tried in hundreds of Scottish surgeries. Stafford thinks the technology could be extended to all kinds of off-label prescribing, although McLay thinks that this might become too complicated.

Mehlman argues for more radical measures as well. He thinks that if a company earns large profits from the sale of a drug for an off-label use, it should be forced to do trials on that use and seek FDA approval if it wants to continue selling the drug. "If manufacturers had more obligations to monitor and test off-label uses, then in return they might be able to talk about them more," says Mehlman. "That would be a fair trade-off."

Woosley disagrees, saying the expense would drive companies out of business. "I think that would be the death of the industry," he says. He argues instead that there should be more government funding for research on off-label usage, and

that technology should be playing a much more effective role in establishing the safety of all drugs, whether off-label or not. "It amazes me that you can get on the internet and find out how many suitcases an airline lost this month, but you cannot find out how many people were harmed by a medication," says Woosley. He thinks doctors should record poor drug outcomes in a national computer network that would flag up common problems.

Everyone agrees that vigorous improvements in surveillance of drug prescriptions, and of what happens to the patients who receive them, are essential to drag drug prescribing towards a more evidence-based footing. The current progress is inadequate, Stafford says. Over the coming year he plans to calculate the financial cost of all the new drugs prescribed off-label in the US to people who might not benefit from them at all. Perhaps that mountain of dollars will finally spur some action.

The right to know

You might think that your doctor would at least have to tell you before prescribing a drug not proven to help treat whatever ails you. After all, doctors are obliged to obtain your informed consent for a treatment, explaining its potential benefits and risks, and outlining any alternatives. But that does not necessarily include telling you a drug or device is off-label, as court cases in the US have consistently ruled.

One case occurred in the late 1990s, when more than 2000 patients in the US complained that bone screws used in their spine had injured them. The Food and Drug Administration had only approved the screws for long, smooth bones like those in the arms and legs. Some of the patients tried to sue the surgeons on the grounds that because they failed to disclose the off-label status of the screws when used in the spine, they did not obtain informed consent. But the courts ruled otherwise. They argued that the off-label status carries no medical information and does not imply that a doctor is doing something new or risky.

From issue 2562 of New Scientist magazine, page 38-41.

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