



SENSE ABOUT SCIENCE
MAKING SENSE OF DRUG SAFETY SCIENCE
Investigating the science of side effects

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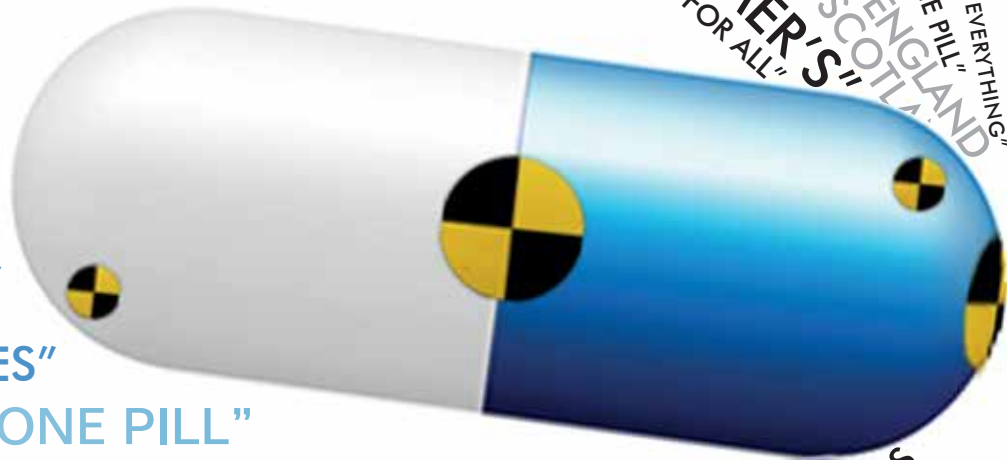
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"SYMPTOMS IN MINUTES"
"CURE WITH JUST ONE PILL"
"TODAY THANKS TO MAIL CAMPAIGN"



"DRUG TO CURE ALZHEIMER'S"
"MIRACLE HEART PILL FOR ALL"
"DRUG APPROVED IN ENGLAND AND WALES BUT NOT SCOTLAND"
"FIGHTING CANCER WITH JUST ONE PILL"
"RAISE A GLASS TO THE 'RED WINE PILL' TO CURE EVERYTHING"

SIDE EFFECTS
"FROG SKIN HITS BIG C"
"E TO FIGHT BIG C - RAVE DRUG AIDS WAR ON DISEASE"
"DRUG 'CAN REVERSE ALZHEIMER'S SYMPTOMS IN MINUTES"
"THE VACCINE THAT COULD HELP BEAT 70% OF CANCERS"

INTRODUCTION

Investigating the science of side effects

Most medical research aims to discover more about health and to find new ways to treat or prevent diseases. Within this, the science of how to make drugs safer has received relatively little research funding and attention. This is despite the fact that side effects (known as adverse drug reactions) are both a big public health concern and a major barrier to the development of new medicines.

Drug safety became a focus of public interest in the 1960s when thalidomide – a drug prescribed for morning sickness – was found to cause birth defects. In 2006 drug safety again came to wider attention following a clinical trial that tested an antibody drug from the company TeGenero Immuno Therapeutics. This resulted in six volunteers being hospitalised from near-fatal side effects. It led to calls for greater support for drug safety science.¹ Even the most beneficial medicines can cause side effects, which is why they are monitored for safety. A UK study that followed 18,820 patients suggested that 1 in 16 hospital admissions are due to drug side effects and that approximately 8000 beds in NHS hospitals are occupied by patients suffering from drug side effects on any one day. Most of these were predictable from the known pharmacology of the drugs and their interactions.²

Side effects are also responsible for many promising drugs being dropped at the development stage or in clinical trials. And once a drug is licensed and being prescribed in the general population, if severe side effects appear and regulators decide that the harms outweigh the benefits, it is withdrawn.

However, researchers could develop more tests to predict who will experience side effects, which would allow a beneficial drug to continue and be used by people who are not at risk. More generally, new funding of drug safety science is opening up our understanding about what gives rise to side effects. In 2008 the Centre for Drug Safety Science, funded by the Medical Research Council, was established in the UK as a joint venture between the Universities of Liverpool and Manchester. It brings together a critical mass of knowledge and technologies to advance our understanding of side effects, the harm they can cause, and to provide solutions.

Drug safety researchers want this knowledge to be applied to the very early stages of drug development and to the ways that drugs are administered. In the coming pages we look at some patients' frustrations about side effects, discussing why they happen and what could be done about them.

¹ Department of Health. Expert Group on Phase One Clinical Trials. Final report.

² Pirmohamed M et al Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ* 2004; 329:15-19



NEIL FRENCH
MRC Centre for Drug
Safety Science



DOMINIC WILLIAMS
MRC Centre for Drug
Safety Science



TRACEY BROWN
Sense About Science



EMILY JESPER
Sense About Science

Note on terminology:

We use 'side effects' to mean adverse drug reactions (ADRs). Researchers prefer the term adverse drug reaction because 'side effects' can also mean good effects (Viagra started life as a potential angina treatment, its beneficial side-effect led to it becoming a treatment for impotence). We are using 'side effects' in the text as it is easier to read and matches everyday use. We are also using drug and medicine interchangeably – researchers talk about drugs but in this document they mean the same thing.

Sense About Science is grateful to all those who have read through the document or helped on specific points, including, Professor Jeffrey Aronson, Heather Doran, Dr John Emsley, Dr Mike Fitzpatrick, Dr Indrayani Ghangrekar, Anita Hanson, Dr Martyn Lobley, Dr Alan Norris, Joe O'Meara, Dr Emma Welsh.

SENSE ABOUT SCIENCE

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NEW MEDICINES

The majority of medicines in development never make it to pharmacists' shelves. News stories about potential wonder drugs usually ignore the hurdles that drugs must overcome to move from the lab into the pharmacy. Sometimes headline grabbing stories are based on very early research results, which can be misleading.



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CLINICAL TRIALS: BALANCING THE RISKS AND BENEFITS OF MEDICINES

All drugs have potential side effects. We are learning more about how to identify them from both old and new drugs, which will influence how scientists and health officials weigh the risks of harm against the chances of benefits. This is achieved through a series of clinical trials, where the safety and efficacy of a drug is tested. Then regulators must decide whether or not to license the drug.



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SIDE EFFECTS

Some side effects are mild annoyances; others can be life threatening. Can side effects be predicted? Here we look at what actually happens in the body when side effects occur, including the role of the liver and some examples of drugs and their side effects.



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WHY DO SIDE EFFECTS HAPPEN?

Researchers have identified some of the most common causes of drug side effects, including the quantity of the drug taken and its unexpected effects on tissues in the body. Side effects can also be caused by an interaction of a drug with another medicine or with foods. When we understand side effects, we can do more to avoid some of them. Some potentially beneficial treatments are denied to patients because of a rare side effect but might not need to be; a drug can be reintroduced if we develop ways of predicting who will develop severe side effects.



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MORE INFORMATION

Find out more about further resources and help with questions about drug safety.



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PATRICIA ROBERTS WHO SUFFERED FROM STEVENS-JOHNSON SYNDROME — A LIFE-THREATENING SKIN CONDITION

"When the symptoms started, I had no idea about Stevens-Johnson Syndrome and that it was caused by the drug I was taking. Although it is rare, it can be fatal in just a few hours so you need immediate treatment. I feel passionately that more people need to know about the enormity of this condition so they can get the right treatment quickly enough; but, most importantly, we need prevention.

As more and more drugs become available we need tests to predict who might develop Stevens-Johnson Syndrome as a result of taking a certain drug, to prevent others suffering as I have."

01

Raise a glass to the
'red wine pill'
to cure everything

NASAL SPRAY COULD BEAT HEART DISEASE

New pill stops arthritis pain

DRUG
'CAN REVERSE
ALZHEIMER'S SYMPTOMS
IN MINUTES'

E TO FIGHT BIG C
- RAVE DRUG AIDS WAR
ON DISEASE

NEW MEDICINES

News of a medical breakthrough inevitably raises our hopes that a new treatment will become available. But, as people waiting for new treatments know only too well, drugs that look promising in early research rarely reach the pharmacists' shelves. For every 100,000 chemicals researched, only four are eventually licensed for prescription.³

This low outcome is often because early results in test tube experiments or in animal models do not translate into results in humans, despite all those optimistic headlines. But potentially effective drugs are also stopped by safety concerns about other effects the drug might have on the body. Such side effects frustrate both the development and prescription of effective drugs. They frustrate patients who need better treatments or who discover that their treatment for one condition increases their risk of another problem. So why haven't medical researchers reduced or eliminated these side effects?

In some cases, with better knowledge, this may actually be possible. But it requires a considerable development of drug safety science. This is because asking, 'what drug could safely treat this disease?' is not actually one question but many, about all kinds of interactions between the drug, the disease and the body.

³ Caldwell GW et al 2001 Current Topics in Medicinal Chemistry

Each requires different expertise, research and better information sharing. Knowing more about the way that drug safety science is now developing will give you a clearer and more realistic view of how new treatments can be developed.

TO DEVELOP A DRUG, FIRST UNDERSTAND THE DISEASE

Researchers need to understand what the disease is doing in the body – which organs, systems or structures are not working as they should and how the disease is using our body's processes – to identify drug targets. Drug targets are points in the disease process which might be changed by a drug or other intervention.

Identifying these targets can be extremely difficult and complex, which is not surprising given the many causes of disease: infections, genetic predispositions, ageing, stress and toxins. Diseases can be short-term such as infection by a cold virus, or long-term (chronic) and potentially life-threatening such as diabetes. And there are many types of drug intervention that might be considered: to prevent disease, cure disease, inhibit its spread, reduce its symptoms or a combination of any of these.

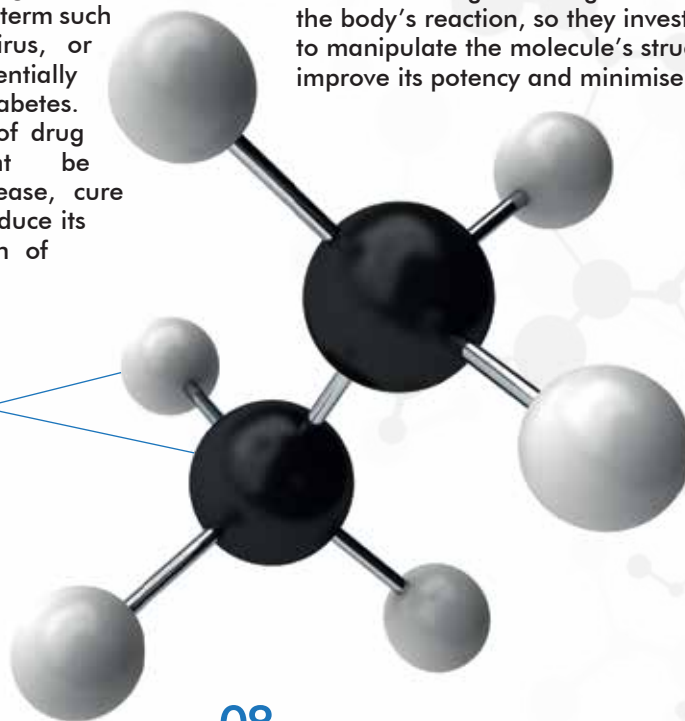
When two or more atoms join together, it is called a molecule. A compound is a molecule that contains at least two different elements, such as carbon and hydrogen

DISCOVERING THE DRUG

Once the drug target has been identified, **medicinal chemists** try to create new compounds (see image below) that act on the target and interfere with the disease process. For example, drugs called antagonists are designed to block the actions of molecules that cause a disease and interfere with their effects.

Scientists sometimes look for ideas for new drugs in plants, marine life and other parts of nature where a molecule is being produced that affects an organism's behaviour. They work out how to cultivate these natural products or to make them from scratch in the lab.

The structure of a molecule influences how it works and the effect it has in a body. Pharmaceutical chemists understand how structural changes to drug molecules affect the body's reaction, so they investigate ways to manipulate the molecule's structure to improve its potency and minimise side effects.



WHAT WILL THE BODY DO WITH THE DRUG?

Pharmacologists investigate where in the body a drug would act and predict the effects a drug might have in humans. A compound has the potential to become a new medicine if it acts selectively on the drug target but has minimal effects on other processes in the body.

This can also be complex because the body and the drug interact in a two-way, dynamic process. All humans and animals have developed efficient multi-purpose systems to absorb, distribute and eliminate or metabolise (change) chemicals in the body. Pharmacologists look at:

- how the drug affects the body (pharmacodynamics); and
- how the body processes the drug and changes it (pharmacokinetics).

Drug metabolism scientists design tests to study how these pharmacokinetic processes affect medicines. It is crucial to understand how drugs are absorbed, travel round and leave the body. If the drug is a tablet, for example, it needs to be absorbed into the blood stream from the small intestine. After it has circulated, it needs to be broken down via metabolic pathways, usually in the liver, and passed out in urine.

Understanding how a drug might act in all these processes helps the design of drugs that are distributed efficiently and remain active for a sufficient time. It can also help predict the side effects each drug could have.

In some cases the body's own methods of breaking a compound down are harnessed, to convert the drug into a form which is active on the drug's target. For example, when aspirin is broken down in the body, the molecule 'salicylate' is formed. This sticks to, and blocks, an enzyme in blood platelets that makes the platelets less sticky and prevents heart attacks.

TESTING FOR TOXIC EFFECTS ON THE HEART

The risk that drugs will cause cardiac problems is a major concern for pharmaceutical companies. Several drugs have been withdrawn from the market because of a toxic effect on the heart. This has led drug safety scientists to investigate how these effects can be predicted and prevented.

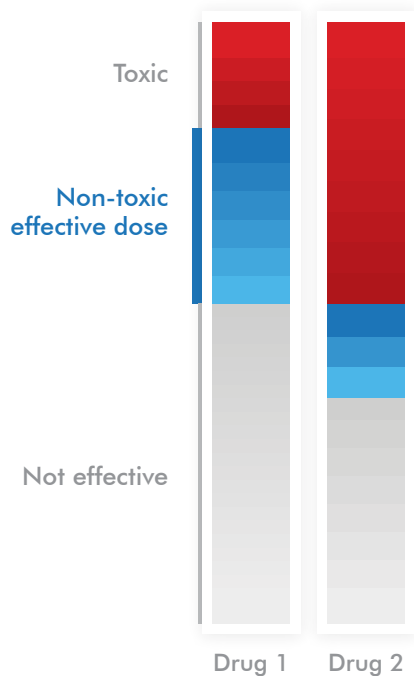
If a drug disrupts the heart's electrical cycle it may cause problems with the way the heart beats (ventricular arrhythmia), which can be fatal. After years of researching the underlying reasons, it was found that this can happen when a drug interferes with hERG channels in heart cells. A standard procedure was then developed to screen drugs in a test tube to eliminate those that could cause this problem from further development.

INVESTIGATING DRUG TOXICITY

Once a drug has been discovered, its safety is assessed, firstly in animals and then in humans. This includes researching its potential to cause harm at different doses.

Five hundred years ago, the physician Paracelsus famously wrote “All things are poison, there is none which is not a poison; only the dose differentiates a poison from a remedy”. He is widely regarded as the father of toxicology.

Toxicologists conduct a battery of tests on every new drug before it is administered to human volunteers or patients. Testing for toxicity does not simply mean testing the drug on the cell which has started the disease. There are many different types of cells, which can interact with the drug and cause side effects. Studies include test tube experiments to determine whether the new drug has potential to damage cells (cytotoxicity) or damage the genetic material in the nucleus of cells (genotoxicity).



ESTABLISHING A SAFE AND EFFECTIVE DOSE OF DRUG

The efficacy of a drug is how good it is at getting the desired response. Drugs are tested for efficacy to work out the dose needed to treat the disease.

Pharmacologists and **toxicologists** work together to establish a dose, based on animal studies, which is sufficient to treat the disease whilst still being safe for patients to take. For new compounds scientists are typically looking for the effective dose for treatment to be at least 10 times lower than the dose that may cause toxic effects, as a safety precaution. This is known as the Therapeutic Index which is often different for different drugs. The higher the value, the safer the drug.

For some drugs the dose needed to be effective is unavoidably much closer to the toxic dose e.g. drug 2 in the figure. This narrow “therapeutic index” makes finding the right dose to give to patients difficult. In some situations, such as cancer chemotherapy, a narrower therapeutic index with an increased risk of side effects might be considered acceptable, bearing in mind the treatment’s potential benefit.

02

Blood pressure drugs
linked to
hyperactivity risk

PROSTATE DRUG LINKED TO MALE BREAST CANCER

Cancer worry over blood pressure drug Epilepsy drug link to birth defects found

CANCER FEARS OVER CHOLESTEROL TREATMENT

CLINICAL TRIALS:

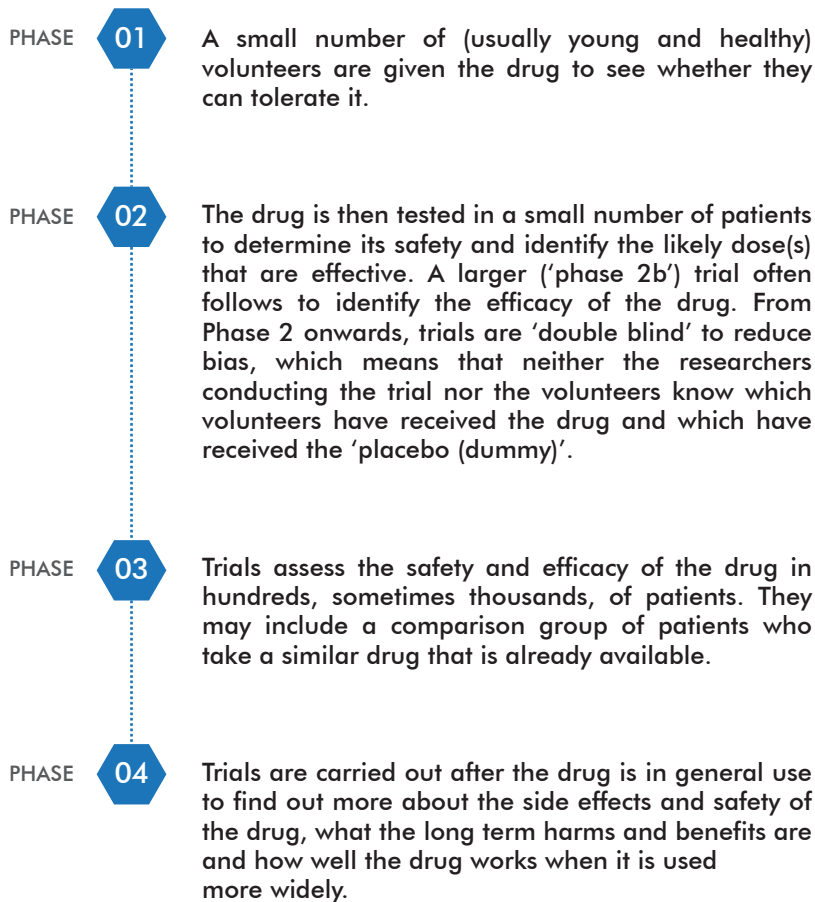
Balancing the risks and benefits of new medicines

Using what is known about the drug being developed, and its interactions within the body and with other substances, drug safety researchers also need to identify possible side effects and to assess their severity at the doses that patients would take. These need to be assessed in clinical trials.

Clinical trials test both the efficacy and safety of the most promising drug candidates, providing initial data about the new drug, which can be used to decide whether its benefits are likely to outweigh its harms. These data are used both to decide whether to proceed with further clinical trials and also later by drug regulators to decide whether the drug should be licensed (it must be at least as effective as currently available drugs).

For safety reasons, before a drug is tested on any humans, preclinical studies are carried out on animals in order to learn more about any toxic effects the drugs may have. Although some consider the use of animals in research unacceptable, their similar anatomy and physiology means that until alternatives can be found, their use in drug development is compulsory. Once researchers are satisfied with the safety/toxicity of a drug in animals, human trials can start.

CLINICAL TRIALS ARE SPLIT INTO PHASES:



After Phase 3 clinical trials, if the outcomes are good, **regulators** have to decide whether to license the drug. Drugs with side effects can be licensed but the beneficial effects must outweigh the risks of harms. The decision takes into account the following:

- the type of illness being treated;
- the improvement offered by the drug;
- the intensity of side effects;
- the likelihood of serious side effects; and
- the possibility of predicting who is most likely to experience serious side-effects.



Once a drug is licensed in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA), anyone can report any side effects that they *suspect* may have been caused by medicines or vaccines, using the Yellow Card scheme run by the regulator; you don't have to *prove* that the medicine was responsible for the harmful event in order to submit a report. Information submitted on Yellow Cards is collected by MHRA and provide a valuable resource for scientists to identify emerging drug safety issues.

YellowCard[®]
Helping to make medicines safer

When treating life-threatening illnesses, more severe side effects are acceptable if the drug could cure or significantly prolong life. For example, chemotherapy can kill cancer cells and lead to recovery, so the risk of severe side effects is accepted.

A drug may also still be licensed if a very small number of people respond badly during a trial. Doctors will be made aware of the risk so that they can monitor patients or avoid prescribing the drug for people who are particularly at risk.

Regulators use the results of the tests to evaluate the safety and efficacy of drugs across whole populations, and to determine the guidance that should be given to doctors and patients about when and how the drug can be used. Regulators can review a licence if new information comes to light after the drug is in general use, and make further recommendations to improve the benefit-risk ratio of the drug, or if this is not possible, withdraw the drug.

While researchers and drug companies are asked to supply all relevant information to regulators, there is no consistent mechanism to ensure that this happens and research has shown that many clinical trials on medicines in current use were not registered or reported⁴. However, this is set to change, with significant improvements to transparency in the international regulation of clinical trials and drug approvals.

The licensing system is designed bearing in mind the whole population and can therefore feel unfairly restrictive to individuals. For example, some people may feel that their disease is so bad that they would be willing to endure more uncomfortable side effects for a lower chance of benefit than regulations allow for. This tension is difficult to resolve, but with the development of drug safety science we are at least able to learn more about which people are likely to be affected badly by a drug's side effects and this will make the decisions about restrictions more accurate.

⁴ Ross JS, Mulvey GK, Hines EM, Nissen SE, Krumholz HM. Trial Publication after Registration in ClinicalTrials.Gov: A Cross-Sectional Analysis. *PLoS Medicine* 2009 8;6:e1000144

03

**AT LAST,
A LOW-DOSE
HRT PILL**
'WITHOUT ANY SIDE EFFECTS'

**STATIN SIDE-EFFECT
RISK UNCOVERED**

Brittle bone drugs
'raise the risk of
eye disease'

Heartbeat risk for thousands
taking osteoporosis drug

**MIXING MY MEDICINES NEARLY MADE ME
BLEED TO DEATH**

SIDE EFFECTS

$\frac{1}{10}$

Very common

More than one in 10 people
are likely to have the side effect

$\frac{1}{100}$

Common

between one in 10 and one
in 100 people are affected

$\frac{1}{1000}$

Uncommon

between one in 100 and one
in 1,000 people are affected

$\frac{1}{10000}$

Rare

between one in 1,000 and one
in 10,000 people are affected

$\frac{1}{10000+}$

Very Rare

fewer than one in 10,000
people are affected

All drugs have the potential to cause side effects. Known side effects are listed on the information leaflet supplied with a medicine. They are categorised by the World Health Organisation as above.

COMMON SIDE EFFECTS

Most of the common side effects are mild and can be inconvenient or upsetting but are not harmful to health.

They can often be predicted before clinical trials because of what is known about how the drug will work in the body. They might be integral to the way a drug works, such as some of the anti-allergy drugs for hay fever, which cause a dry mouth and drowsiness as part of the way they stop the body's immune response to pollen. The trials are then used to observe them to find out more about their intensity and frequency.

Clinical trials can also reveal common side effects that have not been predicted, although this is less usual. Unless a clear understanding of their mechanisms and causes is established, the drug is likely to be discontinued. Drug safety scientists investigate the structure and interaction of these compounds to try to discover the mechanism and inform future drug development.

It is not always obvious whether mild effects experienced by patients in clinical trials are due to the drug or to the disease itself, or even to the experience of being in a trial. This is one reason why it is important that in clinical trials people are split into groups receiving the drug and groups receiving a placebo, to compare what happens.



MARTYN LOBLEY
GP and medical journalist

"Show me a drug with no side effects and I'll show you a drug with no benefits. When you take a medicine you're entering into a bargain. The prescriber, to the best of their knowledge, gives you a medicine that will do you more good than harm, but you have to accept the risk that it may do you more harm than good. For some medicines, we understand the risks and can mitigate them, but for others the knowledge is just not there yet."

RARE SIDE EFFECTS

Rare side effects (occurring in fewer than 1 in 1,000 patients) may not emerge until a drug has been marketed for several years and many patients have been exposed to it. Because clinical trials are expensive to run and cannot include tens of thousands of people, they cannot represent real-life experience in every last detail so they don't pick everything up. This is especially true for effects that are only found in a small subset of the population, such as people who have an unusual genetic condition or who have an underlying disease (such as liver or kidney disease) that disrupts the usual way in which the drug is eliminated from the body.

Whether marketed drugs that are later found to cause severe, rare side effects continue to be prescribed depends on the nature and severity of the disease and the availability of other treatments.

If the effect is not severe and is understood, doctors will be informed of the potential problem so that they can decide whether the drug is suitable for individual patients and information is added to the medicine's label. However, almost all cases of rare side effects reported at this stage are not predicted from the mechanism of the drug or from the pre-clinical toxicology and human volunteer studies. They are generally severe, even life-threatening, reactions.

Drug safety research has to look at both common, rare and very rare side effects. If a drug is withdrawn because one person in 10,000 suffers a serious, very rare effect, 9,999 people lose the use of an otherwise safe and effective medicine. By understanding more about these rare side effects, researchers are seeking to avoid this happening.



HOW THE BODY DEALS WITH MEDICINES

Drugs and the liver

Most drugs reach the blood via the small intestines. After a drug has circulated in the bloodstream it arrives at the liver, where enzymes turn it into chemicals that can then pass to the kidneys and out in the urine. The liver is the main organ to break drugs down. It has a very high concentration of drug metabolising enzymes (proteins that break substances down).

Poor liver function can impair this process, so people with liver problems are more restricted in the medicines they can take. As some drugs can pass out in the urine without being changed, poorly functioning kidneys are also sometimes a problem. They can cause a build-up of the drug in the body, which may be harmful.

Various natural or environmental factors can increase or decrease the rate of metabolism (the rate at which the drug is changed). Physiological factors include age, gender, genetics, intestinal flora (bacteria in the gut) and nutrition. As a general rule, drugs are metabolised more slowly by newborn babies and elderly people. Drug interactions (where a drug's activity is affected by food, drink, a supplement or another drug) also have a large influence on the rate of metabolism by the liver enzymes.

EXAMPLES OF DRUG SIDE EFFECTS

Nonsteroidal anti-inflammatory drugs (NSAIDs) and gastritis

The long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, can cause gastritis (inflammation of the stomach lining). The stomach lining may be "eaten away," leading to sores (peptic ulcers) in the stomach or first part of the small intestine. In most cases, gastritis does not cause permanent damage.

The heart and anti-diabetic agents

Rosiglitazone, a medicine designed to treat diabetes, was withdrawn in the EU in June 2010 after it was shown to be associated with an increased risk of heart attack and stroke in patients aged 65 years or older. The precise mechanism underlying this has not been discovered.

The heart and anti-cancer agents

An association has been seen recently between a new type of anti-cancer agent and heart problems.

These anti-cancer agents, known as kinase inhibitors have been developed to interfere with kinase proteins that are present at high levels in cancer cells. But because the kinase proteins are also present in healthy heart cells, the drugs can interfere with their normal action, so it may prove difficult to remove the risk even with attention from medicinal chemists.

The central nervous system and a drug for obesity

A number of the available obesity drugs are known to cause mild central nervous system side effects (such as drowsiness, anxiety and mood changes) although the anti-obesity agent, rimonabant was removed from the market in 2009 after reports of severe depression and suicidal thoughts. To some extent the central nervous system side effects were predictable since the target for rimonabant is the cannabinoid receptors, which are fairly widespread throughout the brain.

In some cases, medical researchers can eliminate side effects by changing the structure of the drug. Other side effects are avoided simply by not giving the drug to people who are most likely to suffer them ('screening out'). For example, aspirin can cause stomach ulcers, so producers, doctors and pharmacists routinely advise people with a history of stomach problems not to take it.

Another route to reduce side effects is to change the way that a drug is taken. An inhaler to deliver a drug to the lungs reduces its effects on the rest of the body. Some stomach effects can be avoided by taking the medicine only after eating. And sometimes a further drug taken at the same time can reduce side effects, such as using mesna to prevent the effect of chemotherapy agents on the bladder.

04

WHY DO SIDE EFFECTS HAPPEN?

Side effects from a drug can happen for a number of reasons:

1. Increased sensitivity to a drug
2. Increased exposure to a drug
3. The drug has unexpected effects on tissues in the body
4. The drug provokes a dangerous immune reaction ('hypersensitivity')
5. Interactions with other drugs, or even food or drink
6. Genetic and environmental factors

1. Increased sensitivity to a drug

Some people are simply more sensitive to a drug and so a dose of a drug that is well-tolerated in most people may cause problems by being "too effective". For instance, the usual starting dose of drugs used to treat hypertension (anti-hypertensives) can lead to a large drop in blood pressure and dizziness in some patients.

2. Increased exposure to a drug

Underlying conditions such as liver or kidney disease (or drug interactions, see below) can lead to the patient having a larger concentration (or a longer exposure) of a drug in their body than was anticipated from the dose that was given. This can lead to the development of significant side effects.

3. The drug has unexpected effects on tissues in the body

Almost all drugs can interact with proteins or other molecules in the body besides those it was designed to target. In most cases these alternative interactions have no clinical effects at all and can be ignored. However, occasionally they result in a side effect. For example, the anti-histamine drug terfenadine (Triludan) was found to be associated with fatal arrhythmias (subsequently leading to its withdrawal from market) because it inhibited the potassium channel in the heart (known as hERG).

Another example is sildenafil (Viagra), used to treat erectile dysfunction; it targets an enzyme present in the eye as well as the penis, which affects the function of the retina leading to blue vision.

4. The drug provokes a dangerous immune reaction ('hypersensitivity')

Hypersensitivity reactions (or allergic reactions) sometimes occur in response to administration of some drugs to certain individuals. In some cases, hypersensitivity reactions such as a rash are common and manageable. In other cases though, hypersensitivity reactions can be severe and life-threatening—for instance anaphylactic shock or the skin disorder Stevens-Johnson syndrome. Such reactions typically occur in patients with a certain genetic predisposition and in some cases (for example with abacavir which is used to treat HIV), it is possible to predict which patients are going to develop the reaction, and avoid that drug.

5. Interactions with other drugs, or even food or drink

Drugs can interact with food and drink, with dietary supplements such as vitamins, and with other drugs, including herbal remedies such as St John's Wort. These interactions can result in a fundamental change in how the drug is handled by the body making the effect of the drug more powerful or less powerful or increasing side effects.

6. Genetic and environmental factors.

In all cases above, an individual person's genetic make-up can influence whether or not a side effect occurs and the severity of a side effect if it does occur. Environmental factors, for example a viral infection, can also contribute to the development of a side effect.

Pharmacists play an important role in talking to patients about harmful drug interactions, allergies and side effects. They advise on food, drink and activities to avoid while taking a medicine, what to do if you miss a dose and when a concern you have raised requires a call to your doctor.

COMMON DRUG INTERACTIONS

Drugs with herbal medicines

St John's Wort is a traditional herbal medicine that some people take to relieve depression. However, it is well known that it can reduce the effectiveness of the contraceptive pill and drugs used to suppress rejection of a transplanted organ. St John's Wort causes the liver to produce more enzymes, which can change the chemical structure of certain drugs, effectively preventing them from working.

Drugs with dietary supplements

Taking extra Vitamin K with a blood-thinning (anticoagulant) medication such as warfarin can reduce the effectiveness of the medication, putting the patient at risk of blood clotting.

Drugs with food and drink

Grapefruit juice contains chemicals which inhibit the enzymes that help remove many drugs from the body. This can lead to increased amounts of these drugs in the body. For example, grapefruit reduces the ability of the liver to breakdown some statins, which are taken to lower cholesterol. The resulting increased concentrations of statins in the body can lead to side effects that cause damage to muscles.

Cheese contains a naturally occurring chemical called tyramine, which can cause the release of the chemicals dopamine, adrenalin and noradrenaline. Patients taking monoamine oxidase

(MAO) inhibitors to treat depression will already have higher levels of these chemicals, and one potential side effect of any further increase is increased blood pressure. This is known as the "cheese reaction", and it can be caused by other foods that contain tyramine, including some wines and yeast extracts.

Drugs with other drugs

A **drug-drug interaction** is where one drug affects the activity of a second when both are taken together. This can increase the drug's effect ('synergistic'), or decrease the drug's effects ('antagonistic'), or a new effect can be produced that neither drug produces on its own.

If a patient is taking two drugs and one of them increases the effect of the other, this can lead to side effects. On the other hand, if the action of a drug is reduced, it may cease to have any therapeutic benefit because of under dosing. For example, some drugs used to treat epilepsy can reduce the effectiveness of oral contraceptives leading to unwanted pregnancy.

Drug-drug interactions happen as a result of accidental misuse or lack of knowledge about each of the drugs. But sometimes these interactions are exploited deliberately, to enhance the beneficial effects of a drug or reduce side effects. For example, when ritonavir is taken with other anti-HIV medications it can boost their effectiveness. And combining the antibiotic amoxicillin with clavulanic acid overcomes bacterial resistance to the antibiotic.

INVESTIGATING SIDE EFFECTS

Research into the mechanisms by which drugs cause side effects should put us in a better position to make existing drugs safer to use. It should also make it possible to reduce the side effects of new drugs in development.

We can investigate the mechanisms of drugs that have been withdrawn from clinical use, or those that are still being prescribed but that are associated with a particular side effect.

Penicillins are a good example. They are generally safe, but in some patients they are associated with allergic reactions so it is standard practice to avoid prescribing any penicillin for a patient if one specific type of penicillin was thought to have caused an allergic reaction.

As a result, patients are potentially being denied effective medicines that may not cause harm. However, until we have a test

that can tell whether or not a patient will develop a reaction to a specific penicillin, doctors will have to err on the side of caution and not prescribe any penicillins to that patient. Scientists at the MRC Centre for Drug Safety Science hope that by understanding how certain penicillins cause allergic side effects they will be able to develop such a test.

Another drug associated with skin reactions is the anti-HIV agent, abacavir. Although effective against HIV, the drug was being prescribed less and less because it was linked to severe skin reactions, such as hypersensitivity reactions. Further research has since uncovered that only patients with a specific genetic variant were susceptible. Once this was identified, a genetic test was developed to screen for patients with the variant. In this way, the numbers of patients suffering from severe rashes was dramatically cut, and abacavir continues to be used as an effective drug.

Research

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THE FUTURE

The problems are not straightforward so, more and more, they are being tackled by large multi-disciplinary teams that can bring many kinds of experience together. In one case, scientists in the Centre for Drug Safety Science are leading a large European group to develop new laboratory tests to predict whether compounds that are being developed into new drugs are likely to cause liver injury (www.mip-dili.eu). In another, a large global effort, the International Serious Adverse Events Consortium (www.saeconsortium.org) is collecting DNA samples from patients who have suffered from serious drug side effects in order to identify genetic risk factors.

The efforts described above, together with the creation of centres, such as the Centre for Drug Safety Science in the UK, will help to unpick the mechanisms of serious side effects. The information from these can be given to doctors, who will be able to prescribe drugs more safely if they know which patients are likely to react badly to particular drugs. The information will also be fed back into drug development.

Researchers in drug safety science believe that this combination of better coordination, more information, communication between disciplines and new research into side effects will result in effective drugs being retained, and more effective drugs being developed and available to more people.

05

MORE INFORMATION

REGULATION AND SIDE EFFECTS

The **MHRA** is the authority responsible for licensing medicines and medical devices in the UK. In the US it is the **Food and Drug Administration**. Most countries have a similar authority and reporting mechanism.

USEFUL RESOURCES IN THE UK:

NHS CHOICES

has information about interactions between drugs:
www.nhs.uk/medicine-guides/pages/default.aspx

ELECTRONIC MEDICINES COMPENDIUM

if you no longer have the patient information leaflet supplied with your medicine you can find it here:

www.medicines.org.uk/emc/

THE BRITISH NATIONAL FORMULARY

is a reference for prescribers providing advice on the use of medicines:

www.bnf.org

ACADEMY OF MEDICAL SCIENCES

Safer Medicines report:

www.acmedsci.ac.uk/images/publication/SaferMed.pdf

TESTING TREATMENTS

is a book that address the question, How do we

know whether a particular drug, therapy or operation really works, and how well?

www.jameslindlibrary.org/pdf/testing-treatments.pdf

UNDERSTANDING ANIMAL RESEARCH

has a guide to the use of animals in research, *Where do medicines come from?*

www.understandinganimalresearch.org.uk/assets/document/F70D2CC3-FD70-10AB-2A425BB3F09C6EB9/where-do-medicines-c.pdf

BRITISH PHARMACOLOGICAL SOCIETY

a professional association for pharmacologists, has a useful guide: *How do drugs work?*

www.bps.ac.uk/SpringboardWebApp/userfiles/bps/file/Education/HowDoDrugsWork.pdf

THE ROYAL PHARMACEUTICAL SOCIETY

the professional body for pharmacists, has a useful resource: *Fast facts about medicines*

www.rpharms.com/media-centre/facts-about-medicines.asp

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MAKING SENSE OF UNCERTAINTY: why uncertainty is part of science.



MAKING SENSE OF SCREENING: a guide to weighing up the benefits and harms of health screening programmes.



MAKING SENSE OF TESTING: why scans and health tests for well people aren't always a good idea.



I DON'T KNOW WHAT TO BELIEVE: a short guide to peer review.



This guide was produced in collaboration with the MRC-funded Centre for Drug Safety Science. The centre is a joint venture between the Universities of Liverpool and Manchester to bring together a critical mass of knowledge and technologies in order to advance our understanding of Adverse Drug Reactions. www.liv.ac.uk/drug-safety/

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Produced with support from the Medical Research Council



Published in 2013 by Sense About Science, which has final responsibility for the content.



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Company No. 6771027

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