Adverse reactions

Why this subject matters...

Wherever you work in pharmacy, you will be asked about adverse drug reactions (ADRs), as well as a large number of related patient safety issues (e.g. contra-indications). Statistics from hospital medicines helplines for patients show that a high proportion of calls are concerned with side effects.

ADRs occur in 10-20% of hospitalised inpatients and may be responsible for 1 in 1000 deaths on medical wards. Studies suggest about 5% of all hospital admissions are due to ADRs.

Although it has been studied less well, as many as 2% of GP consultations may be due to suspected ADRs.

In practice, pharmacists encounter many clinical problems concerning adverse reactions such as:

- Can drug X cause symptom Y? Is it reversible?
- Which of drugs A, B or C is the most likely cause of symptom Y?
- How should I manage a suspected ADR in this patient?
- This patient has experienced a suspected reaction to drug X. What can I use instead?

PROBLEM + PHARMACIST = SOLVED?

Amoxicillin-induced rash
Courtesy of Skoch3, Wikimedia Commons
Definition

ADRs are great mimickers of disease, causing diagnostic confusion and resulting in unnecessary referral and investigation. Certain disorders are commonly drug-induced and a thorough assessment of drug exposure is particularly important in these cases. Examples of signs and symptoms include rashes, electrolyte disturbances, postural hypotension, confusion, constipation, renal or liver dysfunction, and gastrointestinal haemorrhage. Less common examples include blood dyscrasias.

Shortly, we'll be looking at causality – how to assess whether a medicine is responsible for your patient’s symptoms rather than something else. But first, we need to be sure that we are all talking about the same thing when we describe an ADR. What are the essential features of an adverse drug reaction?

What is an ADR?

ADRs are also known as side effects, and have these characteristics:

- There is some evidence that at least one medicine is responsible.
- The effect is unintended.
- It is harmful, or potentially harmful.
- The reaction is seen at normal doses used clinically (to distinguish ADRs from ‘toxicity’ which describes symptoms of overdose or poisoning).

Some patients have an increased susceptibility to ADRs including the elderly, neonates and children, patients with multiple disease states (e.g. ICU patients, patients with HIV), those with impaired kidney or liver function, and patients receiving polypharmacy. Ignoring manufacturers’ contra-indications or failing to monitor the patient adequately are also common methods of increasing the likelihood of known ADRs.
Assessing causality of adverse effects

You'll commonly be asked whether a patient's signs or symptoms could be drug-induced. You'll be expected to give your opinion or offer advice. Sometimes it is relatively easy to do this, if, for example, the patient is taking only one medicine and there's no evidence to implicate the drug as the cause of the suspected reaction. However, when asked about a patient taking more than one medicine and who has several concurrent medical conditions, it can be very difficult to distinguish which, if any, of the medicines is to blame.

The TRIP system can be used to help determine whether an ADR has occurred. TRIP stands for Timing, Recovery, Independent evidence, Predictability. It's a helpful thing to keep in your head.

### 1. Timing
Depending on the type of adverse reaction, its time to onset can vary from minutes after receiving a drug to months. For example anaphylaxis to IV drugs can begin almost immediately after administration, whereas drug-induced Parkinsonism may take several months to develop. When considering the time interval between drug exposure and onset of symptoms, an understanding of the pharmacokinetics and pharmacodynamics of the drug is required, as well as the mechanism of the ADR.

For withdrawal reactions, the duration of administration and the length of the interval since stopping therapy are important timing considerations.

### 2. Recovery
Do symptoms improve, or resolve completely, when the suspect drug is stopped? This is called de-challenge. Many reactions will resolve on stopping the drug; this supports cause and effect but could be coincidental. Does the reaction improve when a specific treatment is given? (e.g. procyclidine to treat dystonia caused by metoclopramide).
3. Independent evidence
Is there another plausible non-drug cause for the problem? The clinical picture may be a manifestation of an underlying disease. For example, before attributing disturbed liver function to drug therapy, other causes must be excluded such as viral hepatitis or biliary obstruction. Is there objective evidence of a link with drug therapy? A re-challenge will cause symptoms to recur if the suspect drug is restarted. Positive re-challenge is strongly suggestive that the drug was responsible. Although deliberate re-challenge is seldom justifiable, in clinical practice it can occur by mistake (e.g. a patient with known penicillin allergy is given co-amoxiclav by mistake).

There are, however, other types of independent evidence such as plasma levels of drugs or measures of drug activity (e.g. INR).

4. Predictability
Are the characteristics of the adverse event consistent or inconsistent with the known pharmacology of the drug? Check whether similar events have been reported previously with the drug or a related drug in the SPC, BNF, or in clinical trials. Knowing more about the reported presentation of the reaction may help you manage it. For example, many adverse reactions are dose-related such as the dose-dependent prolongation of the QT interval caused by citalopram. Some dose-related side effects can be avoided by using a reduced dose.

These criteria provide useful general guidance but they have some drawbacks. For example, with new medicines there may be only very limited data available. Due to the size and controlled nature of pre-marketing clinical trials, only the most common adverse events will be observed and subsequently listed in the SPC at the time of approval. Rare events, if described, may only be encountered by chance: in this situation you will have less information for e.g. the ‘predictability’ element described above.

A positive de-challenge (resolution of symptoms on stopping the suspect drug) is usually a strong indication of iatrogenic disease but coincidences can occur (e.g. rash in a child taking antibiotics may be viral). Failure of symptoms to resolve quickly may not always count against the possibility of an ADR (e.g. regrowth of hair following drug-induced alopecia will take weeks or months).
Managing ADRs

When confronted with an ADR, ask yourself: **is this a dose-related reaction or not?**

**Dose-related reactions** are an extension of the normal pharmacology of a drug. In university lectures you may have heard them being called 'Type A' reactions. For example, some drugs designed to lower blood pressure in people with hypertension can bring it too low if the dose is large enough, and cause hypotension. This is a dose-related reaction. Depending on the circumstances a dose-related reaction might be managed by:

(a) **Stopping the drug** temporarily or permanently (e.g. a serious haemorrhage in a patient taking warfarin), or
(b) **Reducing the dose** (e.g. daytime sedation in a patient receiving amitriptyline for neuropathic pain), or
(c) **Continuing the medicine and treating the ADR** (e.g. constipation in a patient receiving morphine is usually treated with a laxative).

ADRs that are **not dose-related** are more idiosyncratic and unpredictable and include things like allergy. You might have heard these called 'Type B' reactions. Usually, the offending medicine has to be stopped in patients suffering from this type of reaction.

The diagram below summarises some basic options to consider when managing an ADR:

![Dose-related ADR diagram]

These options may or may not be appropriate in an individual patient depending upon the circumstances: it is not possible to generalise. Of course, how you manage a reaction in practice depends on many factors related to the patient concerned, such as:

- The severity of the reaction.
- Whether you are certain that you know which drug is responsible.
- The consequences if you stop the offending medicine. Is it safe? What other medicine could be used instead?
- Whether a dose reduction is feasible or practical.
- The ability to successfully treat the side effect.
Your practical knowledge about the management of ADRs increases rapidly as you gain experience, but at the beginning of your career it’s appropriate to ask more senior colleagues for advice if you are not sure what to do. Some of the Information Sources at the end of this tutorial may also assist you.

Talking to patients

There are several situations in which you will talk to patients about ADRs. For example, one common scenario is where someone is already suffering from a side effect; another is when you warn or advise a patient about an ADR that they might experience in the future.

Patients need to be aware of the nature of the ADR (the consequences), how likely they are to be affected, and how to manage it.

Consequences

You should describe ADRs in a way that patients understand: most people have heard of the phrase ‘side effect’, for example, and know what it means but not ‘adverse reaction’ so don’t use that. Avoid jargon, try to use everyday language, and check that patients comprehend what you are saying. You can prompt people with phrases such as "Have I explained that clearly?", or "Would you like me to go over that again?" It's helpful to tell patients that there will be a patient information leaflet that comes with each medicine. There are also helpful websites for patients such as NHS Choices.

Likelihood

It is often beneficial to talk about the likelihood that an ADR will occur at an early stage. This helps a patient to put their risk into perspective. The EU has a classification system for the frequency of ADRs which is used in SPCs and patient information leaflets. It uses two methods to express frequency – words and incidence figures:

- **Very common** ≥ 1 in 10 (e.g. gastrointestinal disorders with metformin).
- **Common** < 1 in 10 but ≥ 1 in 100 (e.g. epistaxis with dabigatran).
- **Uncommon** < 1 in 100 but ≥ 1 in 1000 (e.g. pathological gambling with pramipexole).
- **Rare** < 1 in 1000 but ≥ 1 in 10,000 (e.g. rhabdomyolysis with simvastatin).
- **Very rare** < 1 in 10,000 (e.g. Stevens-Johnson syndrome with ciprofloxacin).
You will need to use your judgement to decide which method(s) of expressing frequency are going to be most appropriate or meaningful to the patient. However, a lot of people are not very familiar with phrases such as "1 in 1000" so you'll need to re-work this into a more patient-friendly description. You might say something like "If we gave this medicine to one thousand patients, we reckon that only one person would get the side effect". Be careful with using percentages instead, as they are often misunderstood too.

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Mitigation

You should advise patients if they need to self-monitor for any side effects, and if there are circumstances where an ADR warrants them seeking medical attention (e.g. haemorrhage when on anticoagulants). You can also advise if there are techniques to reduce the impact of an ADR (e.g. taking paracetamol for a drug-induced headache; taking a medicine after food to reduce GI upset).

Besides offering your professional advice, you need to listen to the patient's own concerns:

- "I don't always take those water tablets. They make me want to wee when I'm out shopping, and I can never find a loo."
- "I'd rather put up with the pain than take morphine. It makes me so sleepy that I'm 'out of it', and can't enjoy time with my family."
- "Can I be honest? That antidepressant didn't work and it just made me feel awful. I took it for two weeks and then gave up on it."

How would you respond to each of these situations?
Many health professionals have a poor understanding of the Yellow Card Scheme and its role in pharmacovigilance, and so pharmacists should ensure that they are familiar with it. If the outcome of a clinical problem indicates that an ADR may have occurred, it is worth suggesting that a Yellow Card be submitted to the MHRA if the reaction meets their reporting criteria. For healthcare professionals the MHRA request that we report:

- All reactions to new drugs, which have an inverted black triangle next to them in the BNF, in MIMS, or in their SPCs. (You can read more about the MHRA’s approach to monitoring of black triangle drugs, and the current list of these drugs is [here](#).)
- Any serious reaction to all other drugs including prescription and OTC medicines, vaccines and herbal products.

Patients, carers, or parents are asked to report any side effect that they, or a person in their care, may have experienced from a medicine. You can report reactions to homeopathic and herbal medicines via the same Yellow Card Scheme as for conventional medicines. There are three separate but complementary processes for reporting incidents related to (1) medical devices, (2) defective medicines, and (3) counterfeit medicines.

Yellow Cards may be completed on paper (copies in back of BNF), electronically via the MHRA’s dedicated Yellow Card website, or via the MiDatabank software that all MI centres in the UK use – ask your tutor or your MI pharmacist to show you how this works.

The MHRA provides some free e-learning for healthcare professionals about the importance of national reporting systems for ADRs. It is a lengthy learning package, so you should allow about 45 minutes to complete it, but it is comprehensive and you can count it towards your CPD record.
Published data

When considering information about ADRs in published studies, don't necessarily simply accept the data that you find. Remember to assess the relative validity of different sources of information:

Clinical trials
These give a helpful indication of common reactions with a guide to incidence, but:

- The comparatively small patient populations involved may mean that serious, but uncommon, reactions are not discovered.
- The patients involved in clinical trials may be highly selective and not representative of the real patient population. Often the elderly and children are excluded, for example.
- The procedures for ADR monitoring and reporting in clinical trials are variable in their rigour, and they may not reflect real life.

Case reports
A case report can raise suspicion about an ADR, and may give helpful advice about how a specific situation was managed in practice. However, it is often insufficient by itself to establish a causal association because:

- A single case report linking a reaction to a drug could be just coincidence, or due to one of a large number of confounding influences.
- There is no comparison group not exposed to the drug to allow for a quantitative estimate of risk.
- There is no reliable denominator of drug-exposed patients from which an incidence rate can be estimated.

Epidemiological studies
Given the limitations of clinical trials and case reports, post-marketing epidemiological studies generally provide the best source of quantitative information on ADRs. These fall into two broad categories:

- **Follow-up (cohort) studies.** Groups defined by exposure status to a particular drug are followed and subsequent events recorded and compared. For example 750 patients on leflunomide are scrutinised for adverse events.

- **Case-control studies.** Groups defined by their outcomes are enrolled and prior drug exposures ascertained and compared. For example, 4,000 patients with upper GI bleeding are investigated in an attempt to identify factors that may have caused it.
Suggested questions

They may not apply to every situation you come across, but there are some questions you should be thinking about in practice.

The Medicine

- Identify all current and recent medication, including OTC products, complementary medicines and potential substance misuse. *It's easy to overlook medicines that have been stopped recently or which have not been prescribed.*
- Establish when the suspected reaction began. Which medicines were started beforehand and what were their start dates? *The timing of when an ADR presents is often an important clue to which medicine is responsible.*
- Has a suspect drug been stopped, and has the ADR improved as a result? *Not all ADRs improve quickly after stopping a causative medicine, but any improvement may help to identify the drug to blame.*
- Is it possible that an excipient in the medicine is to blame for the ADR rather than the ‘active’ ingredient? *Consider additives as a potential cause if you are struggling to find an obvious cause from an active ingredient. (There is a separate tutorial on this subject.)*
The Patient

- Ask for details of the suspected reaction including signs, symptoms, and severity. *You need to know how the patient has been affected and the results of any relevant investigations. You’ll need to clarify vague terms like ‘rash’ or ‘liver impairment’.*
- Consider any patient history of ADRs and/or allergies. *If the patient has experienced a similar reactions with a related medicine in the past, then this may help to show which medicine was responsible.*
- Ask about any relevant medical history (e.g. concurrent illness) and test results (e.g. blood levels of drug; renal function). *Some ADRs may cause deterioration of existing illness; sometimes an existing illness increases the risk of ADRs or makes them more serious (e.g. hyperglycaemia in a patient with diabetes). Importantly, the medical history may also suggest a non-drug cause of the patient’s symptoms.*
- Ask how the patient has responded to any intervention related to the ADR. *Has there been an attempt at e.g. dose reduction or treatment of the ADR?*

Going Forward

- How is it planned to manage the ADR? What alternative medicine or treatment might be suitable? *Is there an existing plan, or can you suggest one. Don’t simply identify the likely causative agent: advise on e.g. what can safely be used instead, and how ADR symptoms can be treated. If it’s not obvious, you’ll need to know what a medicine causing an ADR was being used for, so that you can offer alternatives if it needs to be stopped.*
- Who needs to know about this? *If your advice is to stop, change or reduce the dose of a medicine, does the patient or their carer understand? If it is due to an allergy has this been properly documented in the patient’s notes and have they been told why to avoid the drug in future? Will any prescription changes or monitoring requirements be communicated properly so that the patient’s GP knows about them?*
Information sources

Most SPCs include details of adverse events and their frequency. Don’t just look at section 4.8 (‘Undesirable effects’). Depending on the circumstances, you may need to look in sections: 4.3 ‘Contra-indications’, 4.4 ‘Special warnings and precautions’, 4.7 ‘Effects on ability to drive and use machines’, and 4.9 ‘Overdose’. We have a guide to using online SPCs here.

The MHRA’s Yellow Card data are available online as ‘interactive Drug Analysis Prints’ (iDAPs); make sure you’ve read the interpretation guide first. iDAPs for vaccines are only available upon request from pharmacovigilanceservice@mhra.gov.uk. The MHRA’s useful publication Drug Safety Update is available online with a helpful search facility, and you can also subscribe to it via email to keep yourself up-to-date with major safety issues.

Subscription resources such as Martindale, AHFS Drug Information, Lexicomp or Micromedex, can be valuable. They may give data on the outcome of a side effect (e.g. reversibility, duration) and its management (e.g. treatment options). References are usually provided so you can follow these up if necessary. Consider using Medline and Embase if you can’t find what you need in other sources, but choose your search terms carefully.

Expert clinicians or specialist clinical pharmacists can often give practical advice on complex cases (e.g. a dermatologist’s opinion on a skin reaction).

Be careful about conducting a general internet search for information on an adverse reaction. If you do, you may like to look at our brief guide to evaluating websites about medicines.

Presenting your answer

Once you’ve asked sufficient questions, gathered the information required and assessed it, you’ll need to provide an answer. We can offer you some general guidance on answering clinical problems.
Next steps in learning...

Here are some resources to help extend your knowledge about adverse reactions and advising about their prevention and management in clinical practice:

- **Adverse drug reactions and medicines safety** is concerned with the prevalence and characteristics of different types of adverse drug reactions.
- **Reporting adverse drug reactions** describes how and when to report reactions.
- **Patients and adverse drug reactions** focuses on patients at risk of adverse drug reactions and techniques for improving safety and communicating risk to patients.

NHS Education for Scotland and the Yellow Card Centre of Scotland have jointly produced a range of e-learning modules on adverse drug reactions. If you didn't manage to work your way through all of these earlier in the tutorial then you may like to tackle them now.

Try the MHRA’s learning module on pharmacovigilance which was developed with BMJ Learning. This requires you to register with the site.

CPPE has three Adverse drug reactions e-learning programmes about different aspects of adverse drug reactions. You can choose the one you want from here, or use the links below:

- CPPE also has a medicines safety app developed with UKMI and the NHS England patient safety team. It’s a handy, fun way to learn about key medicines safety issues.

[Last updated: 08 May 2018]
There is a helpful Clinical Knowledge Summary on 'adverse drug reactions'. Use the A-Z listing to find this topic.

On the Medicines Learning Portal, there are other tutorials with a connection to ADRs and safety, including Excipients, Renal, Liver, and Alternative Medicine. You might like to study these.

Finally, you may like to review two additional sources of information about adverse drug reactions that offer you different perspectives:

- The European Database of Suspected Adverse Drug Reaction Reports is run by the European Medicines Agency. Here you can see suspected adverse reactions reports submitted by national medicines regulatory authorities and pharmaceutical companies.

- An interesting resource is the American database DrugInformer, which holds data on suspected ADRs gathered from social media (Facebook, Twitter, user review sites, forum discussions), as well as information from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS).