

Adverse reactions

After completing this tutorial, you will be able to:

- Decide whether a patient's reaction is caused by a drug or not.
- Adopt a practical approach to managing adverse reactions and advise other professionals about them.
- Talk to patients about the risk of side effects, and give them management strategies should they occur.

Why this subject matters...

It is estimated that 1 in 16 hospital admissions are due to an adverse drug reaction (ADR), and they are responsible for 4% of hospital bed capacity. ADRs themselves are also thought to occur in 10-20% of hospital inpatients, and one study found that over 2% of patients admitted with an ADR died, approximately 0.15% of all patients admitted.

Statistics from hospital medicines helplines for patients also show that a high proportion of calls are concerned with side effects.

In practice, pharmacists encounter many clinical problems concerning ADRs 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?*



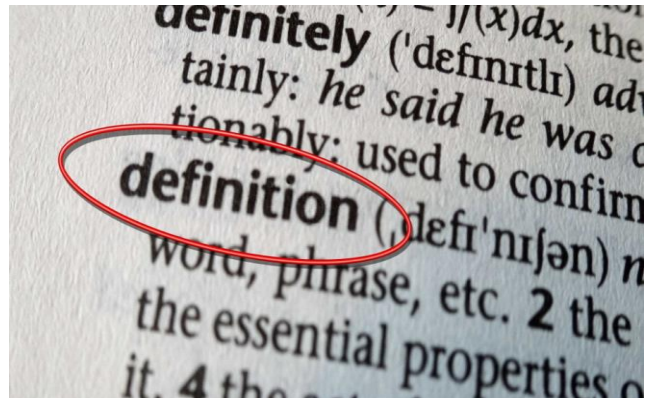
Amoxicillin-induced rash
Courtesy of Skoch3, Wikimedia Commons

Endorsed by



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 signs and symptoms of overdose or poisoning).

Some patients have an **increased susceptibility** to ADRs including the elderly, neonates and children, patients with intercurrent multiple disease states (e.g. ICU patients, patients with HIV), those with impaired kidney or liver function, and patients taking multiple medicines. Failing to follow manufacturers' contraindications or 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, and 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 acronym** can help you to determine whether an ADR has occurred. TRIP stands for **T**iming, **R**ecovery, **I**ndependent evidence, **P**redictability.



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 intravenous 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.

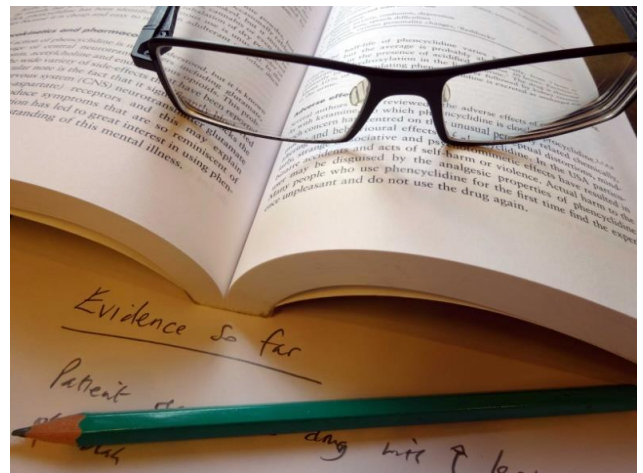
For **withdrawal reactions**, the duration of administration and the length of the interval since stopping therapy are important timing considerations.

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).



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 [SmPC](#) or BNF. 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 SmPC at the time of approval. Rare events, if described, may only be encountered by chance: in this situation you will have less information (e.g. for 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

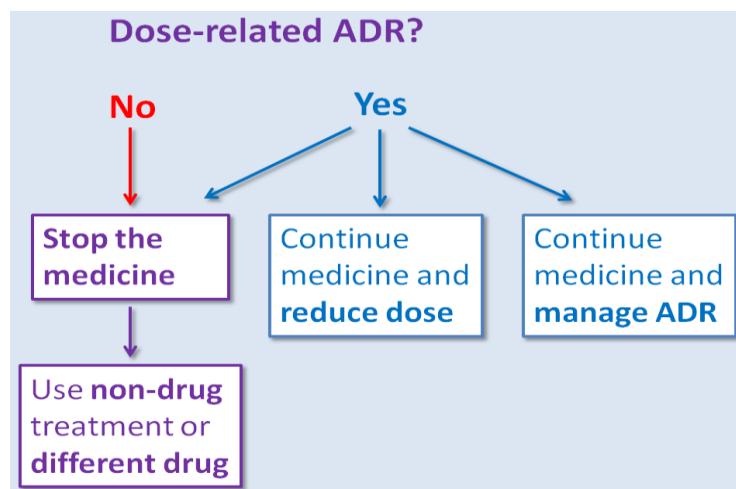
When confronted with an ADR, ask yourself: *is this a dose-related reaction or not?*

Dose-related reactions are an extension of the normal pharmacology of a drug. You may have heard them being called '**Type A**' reactions. For example, some drugs designed to lower blood pressure in people with hypertension can lower it too much 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. 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:



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.

The Type A and B classification system has been extended to include reactions that persist for a relatively long time (**Type C or 'continuing'**) such as lung fibrosis with methotrexate, those that may be relatively **delayed** after drug exposure (**Type D**) such as hepatitis with flucloxacillin which can occur after the drug has been stopped, and **end-of-use** reactions (**Type E**) such as discontinuation syndromes with antidepressants.

Other classification systems have been developed such as DoTS; is the adverse reaction **dose**-related, **time**-related or does the patient have factors that make them more **susceptible** to developing a 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.

Drug allergy

The definition of a **drug allergy** is evolving as we better understand the underlying mechanisms.

The British Society for Allergy and Clinical Immunology (BSACI) previously defined an allergy as an ADR with an established immunological mechanism. However they have broadened the definition to include **any ADR that has the clinical features of hypersensitivity (i.e. rash, angioedema, bronchospasm, hypotension) regardless of the mechanism**. For example, NSAIDs may cause bronchospasm and urticaria but this is usually because of cyclo-oxygenase 1 (COX-1) inhibition and not an immune-mediated reaction: under the newer BSACI definition this is classified as drug allergy.

Having said that, in most cases, drug allergy does involve the immune system and reactions are categorised as either Type 1, 2, 3 or 4 according to the immunological mechanism responsible. The Type 4 category is subdivided further. **Most allergic reactions to drugs are Type 1 or Type 4.**

Type 1 hypersensitivity reactions are caused by the production of IgE after an initial exposure to an antigen such as a drug. This IgE binds to mast cells, found throughout the body, which become 'sensitised' against that antigen. When a second exposure to the antigen occurs, these sensitised mast cells release their contents which include histamine, leukotrienes and prostaglandins. Most allergic responses are localised to the tissue where the allergen has come into contact (e.g. allergic rhinitis symptoms occur where pollen makes contact in the nose and eyes). However sometimes responses may be systemic as is seen with drug-induced anaphylaxis.

Histamine and other mediators released from mast cells may cause

- an increase in epithelial permeability of blood vessels causing **oedema** and **urticaria**
- vasodilation which may lead to **hypotension**
- bronchial smooth muscle contraction which may cause **bronchospasm**

Type 1 hypersensitivity reactions occur quickly and are sometimes called '**immediate**' reactions. The **penicillins** and **cephalosporins** are examples of drugs causing type 1 hypersensitivity reactions.



Type 4 hypersensitivity reactions are also known as '**delayed**' reactions because they develop several days after exposure to the antigen. This category of hypersensitivity reaction is mediated by T-cells, rather than antibodies as in Types 1-3, and is divided into 4 subtypes according to the type of T-cell(s) and cytokine(s) or chemokine(s) involved. Tissue damage and inflammation are caused by release of cytokines co-ordinated by T-helper cells (CD4+), or directly by T-killer cells (CD8+) releasing their cytotoxic contents. As large numbers of T-cells are found in the skin, patients suffering a Type 4 reaction to a drug will present with symptoms that include a rash (e.g. contact dermatitis, erythema multiforme, Stevens-Johnson syndrome). Systemic symptoms may also occur such as fever, and other organs may be involved such as the liver and/or kidneys. Anticonvulsants, antibiotics and ACE inhibitors can cause type 4 hypersensitivity reactions.

The [BSACI](#) and [NICE](#) (2014) have published guidance on managing patients with drug allergy; accurate history taking is essential.

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 **websites** for patients such as the [NHS site](https://www.nhs.uk).

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 SmPCs 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 \geq 1 in 10,000 (e.g. rhabdomyolysis with simvastatin).
- **Very rare** < 1 in 10,000 (e.g. Stevens-Johnson syndrome with ciprofloxacin).



© Crown copyright 2017

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 expect that only one person would get the side effect". Be careful with using percentages instead, as they are often misunderstood too.

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 gastrointestinal 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?

Reporting to the MHRA

The [Yellow Card Scheme](#) run by the MHRA is the UK system for collecting and monitoring information on safety concerns such as suspected side effects or adverse incidents involving medicines and medical devices. The scheme relies on voluntary reporting of suspected side effects or medical device incidents to be reported by healthcare professionals and the public, including patients, carers and parents.

The screenshot shows the Yellow Card reporting website. At the top, there is a yellow header with the 'YellowCard' logo and a search bar. Below the header is a navigation menu with links: Home, About Yellow Card, FAQs, Resources, Campaigns, Drug Analysis Profiles, and Contact Us. A prominent banner states: 'Use the Coronavirus Yellow Card reporting site to report suspected side effects to medicines and vaccines or medical device and diagnostic adverse incidents used in coronavirus treatment'. The main content area is divided into two columns. The left column, titled 'Welcome to the reporting site for the Yellow Card scheme', lists categories for reporting: 'Report a suspected problem or incident:' (with a 'COVID-19' button), 'Side effect to a medicine, vaccine, herbal or homeopathic remedy' (with a 'Side effects' button), 'Incidents involving a medical device including diagnostic tests, software and apps' (with a 'Devices' button), 'Defective medicine (not of an acceptable quality)' (with a 'Defective' button), and 'Falsified or fake medicine or medical device' (with a 'Fake' button). The right column contains a 'Download the Yellow Card App!' section with information about receiving news updates and downloading the app from the App Store or Google Play Store. Below this is a 'Sign in / Register' section with fields for Email Address and Password, a 'Login' button, a 'Forgot your Password?' link, and a 'Register' button.

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 SmPCs. (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, blood factors and immunoglobulins, and herbal products.

In addition, they are also specifically interested in ADRs in children, in the elderly, with biologics or herbal medicines, those that occur as a result of a drug interaction, those that are rare or delayed or cause a congenital anomaly. You can read more [here](#).

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.

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 the back of the BNF), electronically via the MHRA's dedicated [Yellow Card website](#), or via the MiDatabank software that all Medicines Information centres in the UK use – ask your tutor or your MI pharmacist to show you how this works.



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.

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 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.

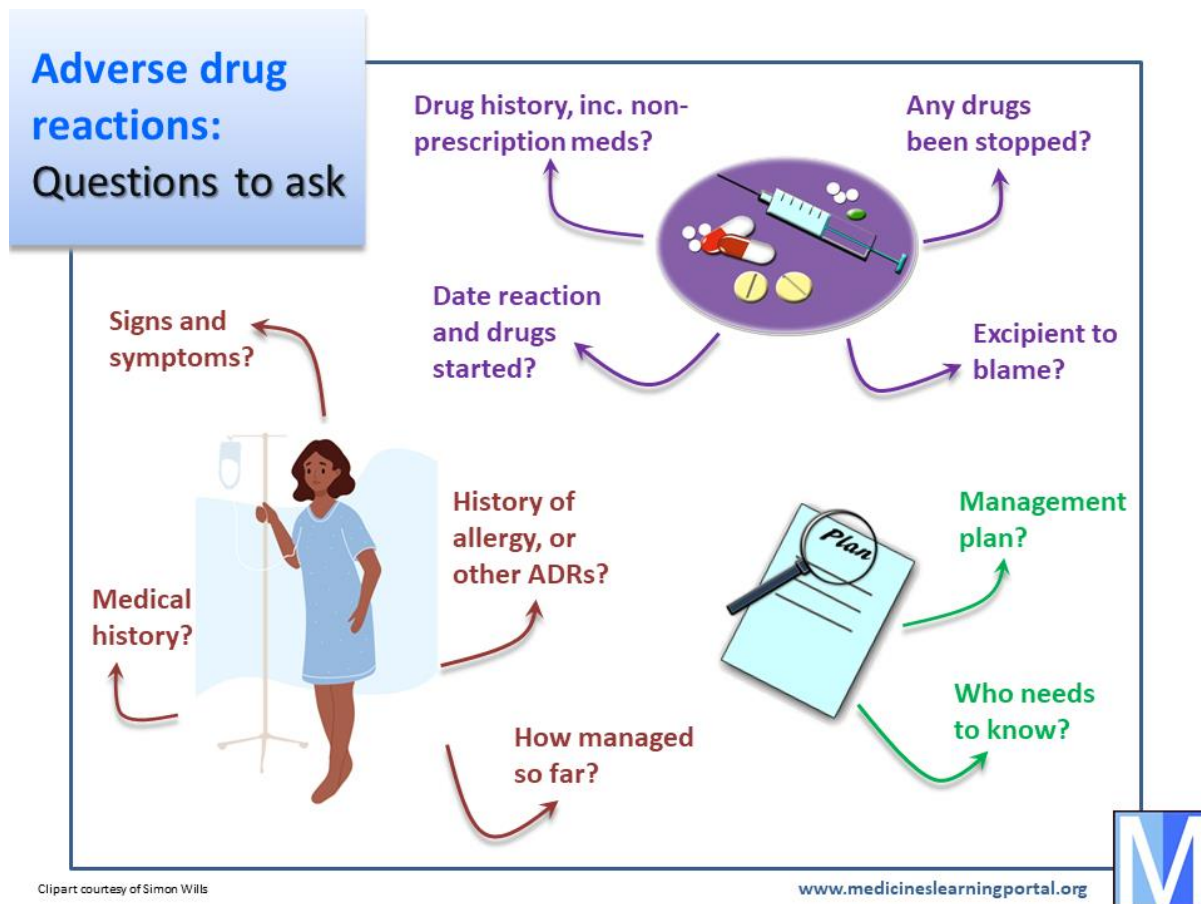


Epidemiological studies

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 gastrointestinal bleeding may be 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 reaction with a related medicine in the past, then this may help to decide 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 the 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 **SmPCs** 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 'Contraindications', 4.4 'Special warnings and precautions', 4.7 'Effects on ability to drive and use machines', and 4.9 'Overdose'.

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**, **Embase** and **Google Scholar** if you can't find what you need in other sources but choose your search terms carefully.

The **MHRA's Yellow Card data** are available online as 'interactive Drug Analysis Profiles' (iDAPs); make sure you've read the interpretation guide at the bottom of the each iDAP first. Note that the likelihood of experiencing an adverse drug reaction when taking a medicine cannot be estimated from the data in the Interactive Drug Analysis Profile. This is because the MHRA have limited information about how many people have taken the medicine without experiencing a reaction. iDAPs for vaccines are only available upon request.



Drug Safety Update

Latest advice for medicines users
The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

Volume 15 Issue 4 November 2021

| Contents | |
|--|---------|
| Yellow fever vaccine (Stamaril): new pre-vaccination checklist | page 2 |
| Adrenaline auto-injectors: reminder for prescribers to support safe and effective use | page 5 |
| COVID-19 vaccines and medicines: updates for November 2021 | page 9 |
| Letters and medicine recalls sent to healthcare professionals in October 2021 | page 11 |

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.



First, we inform of the new pre-vaccination checklist for the yellow fever vaccine. The checklist aims to ensure vaccination is indicated for the intended travel destination and enable vaccinators to identify existing contraindications or precautions in individuals before vaccination.

Next, we provide details of the resupply to the market of Emerade adrenaline auto-injectors and remind healthcare professionals of the important safety precautions when prescribing and advising patients about adrenaline auto-injectors. This advice follows the publication of a report from the Commission on Human Medicines on the effective and safe use of adrenaline auto-injectors for the emergency treatment of anaphylaxis.

The MHRA's useful publication **Drug Safety Update** is available online with a helpful search facility, and you can also subscribe to it via e-mail to keep yourself up-to-date with major safety issues.



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 their prevention and management in clinical practice:



NHS Education for Scotland and the Yellow Card Centre of Scotland have jointly produced a range of [e-learning modules on adverse drug reactions](#)

Try the e-learning module on [adverse drug reactions](#) on the SCRIPT safety site supported by HEE. You will need to log in but access is free with an NHS e-mail address.



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

- [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.



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.

There is a helpful [Clinical Knowledge Summary](#) on 'adverse drug reactions'.

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 [DrugInformr](#), 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).