Interactions

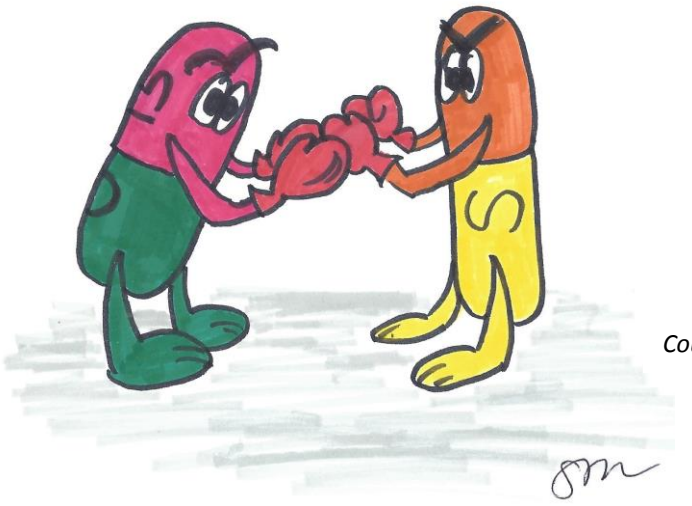
After completing this tutorial, you will be able to:

- Describe common mechanisms by which drugs interact.
- Adopt a practical approach to identifying, managing, and monitoring interactions.
- Talk to patients about drug interactions.

Why this subject matters...

Pharmacists are the NHS experts on drug interactions. Preventing, detecting and managing them is part of their clinical role. In practice, pharmacists are asked about them a lot: interactions are flagged up by e-prescribing systems, and appear in patient information leaflets and in the BNF. Clinicians want to know if these interactions will affect their patient and what to do about them. And that's where pharmacists come in.

Drug interactions can pose a significant risk to patients, although in practice they are a much less common cause of harm than adverse reactions. However, interactions are perhaps recognised less often and the pharmacist's active safeguarding role helps to protect patients.



Courtesy of Siba Majid

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Definition

A drug interaction occurs when the effects of a medicine given to a patient are altered by the presence of another medicine, a chemical, or food. Don't forget that one of the interacting entities involved could be a herbal medicine or a street drug.

Not all drug interactions have an adverse outcome, but for the purpose of this tutorial we will deal only with interactions between medicines that could have negative consequences for patients. These form the majority of drug interactions that pharmacists get involved with.

Mechanisms

Here is a quick refresher on the five most important drug interaction mechanisms:

1. Absorption

One drug decreases the absorption of a second drug from the gut. For example:

- *Some antacids can decrease the absorption of drugs such as ciprofloxacin and iron by reacting with them chemically.*

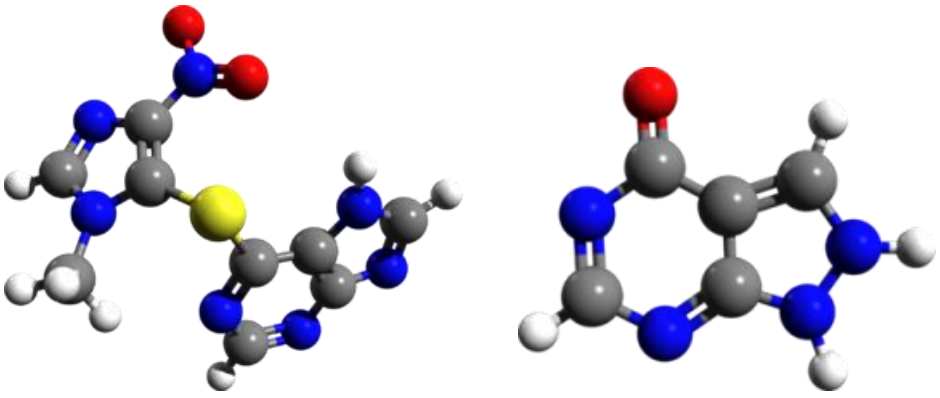
Patients that already have poor absorption due to disease may be at enhanced risk (e.g. patients with Crohn's disease, a short bowel, or cystic fibrosis).

2. Metabolism

One drug increases or decreases the metabolism of a second drug. For example:

- *Rifampicin enhances the metabolism of female sex hormones, making the contraceptive pill unreliable.*
- *Allopurinol inhibits the metabolic destruction of a cytotoxic metabolite of azathioprine, so that it can accumulate to cause toxicity.*

The activity of enzymes that metabolise drugs are subject to genetic control. A poor metaboliser of warfarin for example may require lower doses and be at greater risk of bleeding. So there is also likely to be genetically-related variation between individuals in terms of the severity of some metabolic interactions.



Azathioprine and allopurinol *Courtesy of Giorgiogp2, Wikimedia Commons*

3. Elimination

One drug increases or decreases the rate at which a second drug is removed from the body by organs such as the kidney or liver. For example:

- *Amiodarone reduces the elimination of digoxin by the kidney.*
- *Cholestyramine enhances the biliary excretion of the active metabolite of leflunomide.*

The mechanisms of excreting drugs from the body are affected by age and disease. Elderly patients, for example, often have a reduced renal function so they may be more vulnerable to any interaction that further reduces elimination.

4. Cell transport

One drug affects the movement of another drug across cell membranes. For example:

- *Cicloporin inhibits an organic anion-transporting polypeptide (OATP), and this reduces passage of rosuvastatin into the liver for metabolism. Stain levels rise, which may cause myopathy.*
- *The herb St John's Wort induces the transport protein p-glycoprotein in the intestine and reduces the absorption of digoxin.*

These are relatively newly discovered mechanisms of interaction and we are still learning about them.

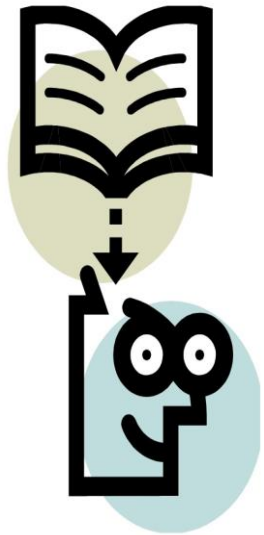
5. Pharmacodynamic

Two drugs have additive or opposing pharmacological effects. For example:

- *NSAIDs cause fluid retention, which may counteract the action of diuretics.*
- *Sedative drugs have additive CNS depressant effects with alcohol.*

The likelihood of a pharmacodynamic interaction being clinically important is influenced by a patient's clinical condition. Sedation, for example, may be particularly undesirable in a patient with a head injury or severe liver disease.

Predicting interactions



An important part of the pharmacist's role is to anticipate when interactions are likely to occur. For example, patients taking lots of drugs (**polypharmacy**) are more likely to experience an interaction.

Another important risk factor to consider is medicines with a **narrow therapeutic range** (*e.g. ciclosporin, lithium, phenytoin, warfarin, digoxin, theophylline*). In patients who take these medicines, an interaction which affects the drug is more likely to be clinically significant. So starting a new drug in these patients always requires a check for interactions.

There are a number of **'alarm bell' drugs** that are particularly liable to interact with many other medicines (*e.g. erythromycin, ritonavir, carbamazepine, fluoxetine, rifampicin, clozapine*). Try to have a mental list of drugs like these to guide you in your practice.

Nonetheless, it is not always easy to discover whether an interaction will or will not occur in clinical practice. If you can't find any published information, you may be able to predict the likelihood of an interaction, using these points as a guide:

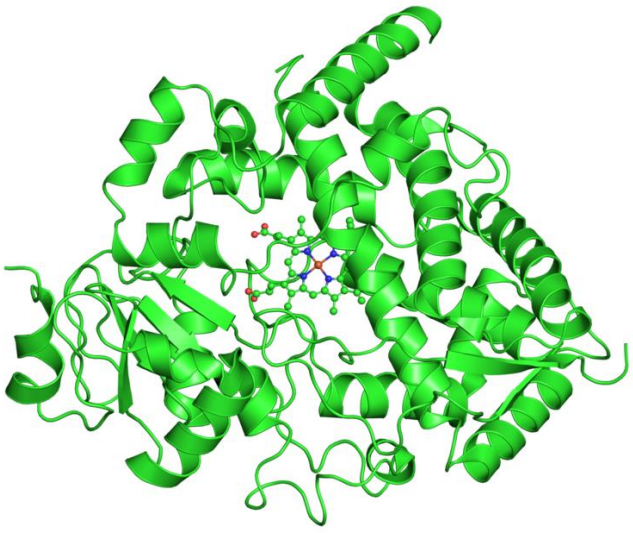
- How are the two medicines cleared from the body? Are they metabolised by the same enzyme? Is one of the drugs known to inhibit or induce it? The SPC will often provide this kind of information.
- Is there any information on how pairs of related drugs behave when given together? *Stockley's Drug Interactions* may assist you with this.
- Do the two drugs have any frequent side effects in common? These effects may be additive when the two drugs are given together. Again the SPC may be valuable here.

Cytochrome p450

A basic knowledge of cytochrome p450 enzymes helps to understand many drug interactions. It is actually a large family of enzymes and each individual one is called an **isoenzyme**. The isoenzymes are named using numbers and letters, and the four most commonly involved in metabolising drugs are:

- **CYP1A2** (*e.g. clozapine, theophylline*)
- **CYP2C9** (*e.g. phenytoin, warfarin*)
- CYP2D6 (*e.g. fluoxetine, tamoxifen*)
- CYP3A4 (*e.g. ciclosporin, carbamazepine*)

Many, but not all, drugs are metabolised by cytochrome p450 and a knowledge of which isoenzyme is involved can make understanding of interactions easier. CYP2D6 is commonly involved, and said to be responsible for metabolising around a quarter of prescription medicines. However, individual drugs are not metabolised exclusively by one isoenzyme, although one usually predominates. Theophylline, for example, is metabolised by CYP1A1, 1A2, 2D6 and 2E1, but 1A2 is the main one. As a result, theophylline is said to be a substrate for CYP1A2.



Structure of CYP3A4 Courtesy of www.ebi.ac.uk

Medicines that make an isoenzyme **more active** are called **inducers**. This means that drugs **inducing** CYP1A2 (e.g. tobacco) will speed up the main route of theophylline metabolism resulting in a shorter duration of action and lower peak plasma concentrations. This may **reduce efficacy**.

Medicines that make an isoenzyme **less active** are called **inhibitors**. Drugs which **inhibit** CYP1A2 (e.g. ciprofloxacin) will slow theophylline metabolism, giving a longer half-life and higher peak levels. This may cause **toxicity**.

If you can't remember the difference between inhibitor and inducer, then try memorising that inhi**bit**ors have **bit**ten the enzyme to stop it working.

When you need to look up whether a drug is an inducer, inhibitor or substrate of cytochrome p450, then the Transformer website is helpful, although it's a technical rather than a clinical website. Type a medicine into the Drug Name box and hit return; you get lots of technical data, but effects on cytochrome p450 are listed halfway down under 'CYP interactions'.

Note that while some enzyme inhibiting or inducing medicines affect the isoenzymes responsible for their own metabolism (e.g. ciclosporin), others can affect completely different isoenzymes or are themselves hardly metabolised at all (e.g. ciprofloxacin).

Induction and inhibition: when it starts and when it ends

How long do these enzyme effects take to begin, and what happens if the drug that causes them is stopped? This is a common question. *Stockley's Drug Interactions* explains it well:

> 'The timing and extent of **enzyme induction** depends on the half-life of the inducing drug, its dose and the rate of turnover of the enzyme being induced. Therefore, broadly speaking, it can take days or even 2 to 3 weeks to develop fully, and might persist for a similar length of time when the enzyme inducer is stopped. This means that enzyme induction interactions can be delayed in onset and slow to resolve...
>
> 'More common than enzyme induction is **enzyme inhibition**. This results in the reduced metabolism of an affected drug, so that it might begin to accumulate within the body, the effect usually being essentially the same as when the dose is increased. Unlike enzyme induction, which can take several days or even weeks to develop fully, enzyme inhibition can occur rapidly, often within 2 to 3 days, resulting in the rapid development of toxicity; however, the effects might not be maximal until the inhibiting drug reaches steady-state. The faster onset of enzyme inhibition is because this process often involves the drug binding with the enzyme, thereby preventing its function, whereas enzyme induction requires increased synthesis of the enzyme (a slower process).'
>
> *Claire L Preston (editor), Stockley's Drug Interactions [online], London: Pharmaceutical Press www.medicinescomplete.com/mc/stockley/current/ (accessed on 20/11/2017).*

Note that some enzyme inhibitors do so reversibly (e.g. fluconazole) so the inhibition wears off as quickly as the offending drug is eliminated. Others have an irreversible action (e.g. erythromycin) so reversal has to wait for the offending drug to be eliminated *and* for new enzyme to be synthesised.

Managing and monitoring interactions

In clinical practice there are a number of strategies by which you can help reduce the chances of an interaction affecting a patient:

- **Prescription review. Screening** by a pharmacist is a significant means by which interactions are prevented, detected, and addressed. **Medicines reconciliation** is also important for ensuring that all medicines taken by a patient are documented, and then any interactions are more likely to be picked up. Addressing **polypharmacy** may reduce the number of drugs taken and thereby lessen the risks of interactions.

- **Choice of drug**. Different drugs in the same class have differing potentials to interact (*e.g. clarithromycin is a potent inhibitor of CYP3A4, but azithromycin is not*). Swapping to either another drug in the same class or a different class of drug with the same indication may avoid an interaction.

- **Withholding one medicine**. Sometimes the safest approach may be to withhold one medicine or delay starting it to avoid an interaction. For example, consider a patient on simvastatin who requires clarithromycin for a chest infection. In this situation, the clinical urgency of treating the infection, may make it acceptable to temporarily stop the statin until the clarithromycin course has been completed.

- **Dose reduction**. Some interactions tend to increase the activity of one medicine fairly reliably. In this situation you may be able to reduce the dose of that medicine. For example, one strategy if itraconazole is essential for a patient on sirolimus, may be to reduce the sirolimus dose and monitor its levels. However, in practice you would seek expert approval and guidance before doing this.

- **Monitoring and communication**. If a potentially interacting combination must be used, knowing the possible outcome may allow the patient to be monitored for potential adverse effects. You need to plan ahead and appreciate where the patient will be if monitoring is required. For example, it's easier to ensure an inpatient is monitored for cardiac side effects than a patient who is due to go home in an hour. Think about who will do the monitoring and how, and talk to the patient or their carer about this as well as healthcare staff.

- **Ask specialists**. Clinical pharmacists in a specialist field often have a good working knowledge of practical ways to avoid, monitor, or reduce the effects of potentially interacting combinations of drugs. Listen to Michelle Cerrato, Lead Pharmacist for Cardiovascular and Thoracic Care at University Hospital Southampton, as she explains how to manage medicines that affect the QT interval.

Talking to patients about interactions

We're going to consider three elements of your approach to advising patients about interactions: What's the potential consequences? How likely is it you'll be affected? What are we doing about it?

Consequences

Explain the interaction to your patient in a clear and meaningful way. What might happen to them because of the interaction? Avoid jargon. For example, be aware that the word 'interaction' itself is not widely understood by most patients. You need to use everyday words. For example: *"We've stopped X because it made your warfarin too strong, and we were worried it might make you bleed. We'll monitor you, but you mustn't take X again."*

Likelihood

When talking to patients about the risk associated with an interaction, it helps if you are clear whether an adverse outcome is:

- Theoretical – some interactions are listed in patient information leaflets or SPCs because it is conjectured that they might occur, not because they've been seen in practice. For example, some drug combinations are theorised as prolonging the QT interval, but the implications for real patients are uncertain.
- Possible – studies suggest that only some patients are affected. Try and quantify the risk if possible. *"Most patients don't seem to have a problem taking these two drugs together, but we know that a few patients can, so we want to be careful."*
- Likely or certain – sometimes the interaction affects the majority. For example, rifampicin reduces the plasma levels of methadone so commonly, that long-term methadone recipients often need a methadone dose increase when rifampicin is started.

In any event, try and contextualise the risk by relating it your patient's personal situation. Spell out the implications for them. Telling patients that an interaction might 'sedate them' isn't that helpful; it's better to explain that you're worried about them having a fall because of it. Sometimes the patient's medical condition or age makes an interaction more of a concern: *"You may be a bit more at risk because your kidneys aren't working well".*

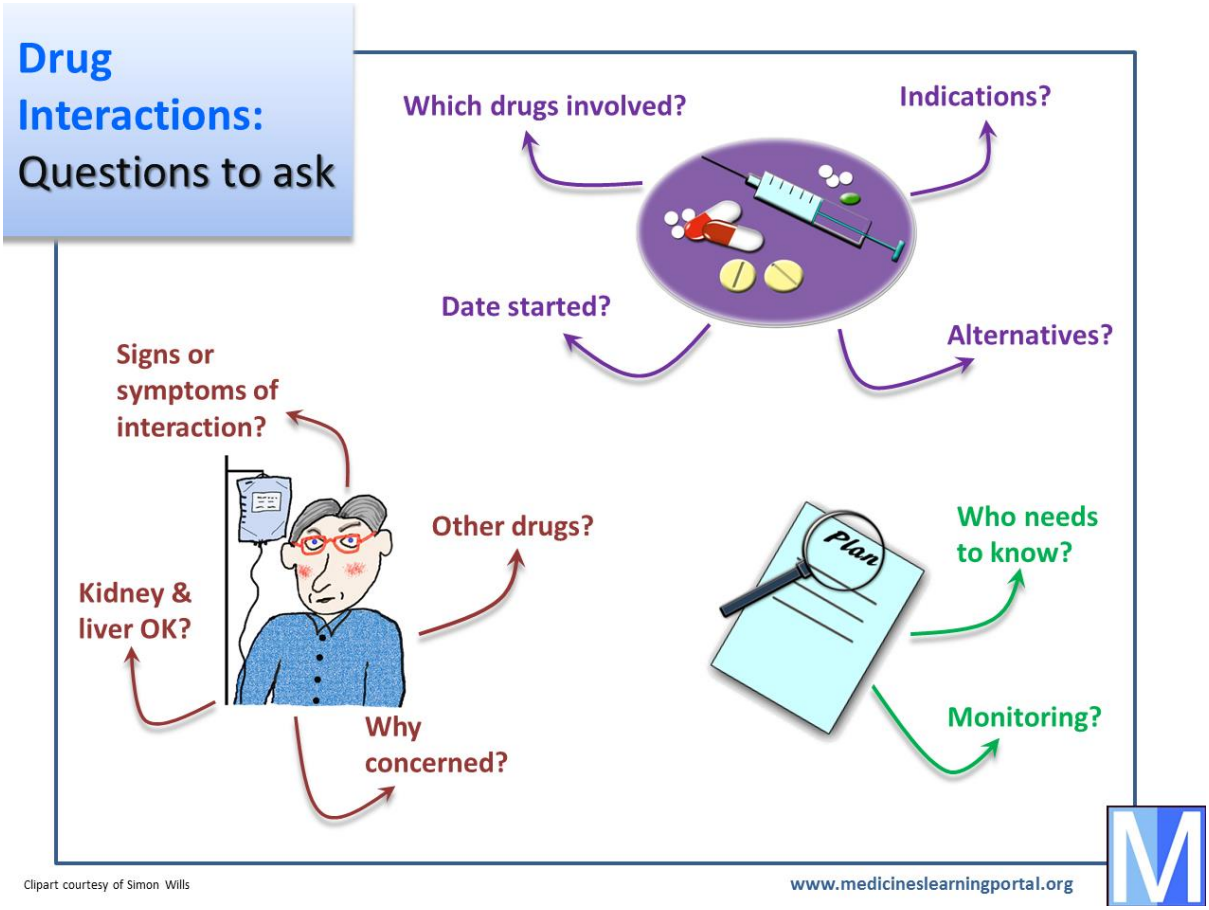
Mitigation

What is being done to reduce the risk of an adverse outcome for the patient? Has a drug been changed or a dose of either drug been altered? Is there any biochemical or other monitoring in place? It's important to ensure that there's a plan that identifies *who* will do the monitoring – GP, outpatient clinic, consultant, patient themselves – as well as *what* they will do.

You should explain the nature of an interaction to the patient and describe what may happen to them if they are affected: what will the symptoms be? You should also explain if they can self-monitor, and what to do if they are affected (e.g. stop drug, see GP, self-treat).

Suggested questions

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



There's more detail on these questions and why they are important, on the next page.

The Medicine

- Which drugs are involved, and is the patient already taking both of them?
  Commonly, a patient already taking one medicine is prescribed a second one which may interact. In practice it's often easier to change the new drug if you can.
- How long have they been taken for?
  If a patient has been stable on a combination for a long time without ill effects there may be no need to change the prescription.
- If there is an interaction, is there any reason why alternative drugs can't be used to avoid it?
  Sometimes alternatives that are less likely to interact have already been prescribed or were not tolerated.
- What is the indication for the medicines involved?
  This enables you to advise on alternative treatment if necessary, and sometimes the indication will affect the remedial action or monitoring required.

The Patient

- If the patient is already taking both drugs, have any problems been identified or investigated?
  You need to know if the combination has already made the patient ill, or if the prescriber is worried about a particular aspect.
- Is the patient taking any other drugs?
  It's important to have the full picture to avoid potential interactions that may have been missed.
- What is the patient's liver and renal function like?
  This can affect clearance which may make the patient more prone to interactions or adverse effects.
- Has a healthcare professional or patient read a warning about the combination?
  Sometimes e-prescribing systems or websites flag up interactions indiscriminately; they are not always relevant.

Going Forward

- If any monitoring would be required who would do this?
  If your advice is to continue with a potentially interacting combination, or to change a medicine, you need to ensure the patient will be monitored by e.g. blood tests, checking efficacy, looking out for side effects. Who will do this? Does a GP know what to do if the patient is going home? You should talk to the patient about this too.

Information sources

Stockley's Drug Interactions tends to offer practical advice on patient management, but it does *not* cover all interactions.

The SPCs for medicines often identify interactions. Make sure you check the Contra-indications, Special Precautions, Undesirable Effects, and Interactions sections of an SPC because relevant information may appear in any of these places. Don't rely on the Interactions section alone. Some interactions may be listed because they could occur in theory rather than being a proven problem in clinical practice (e.g. where cytochrome p450 is a minor part of a drug's metabolism). Use other sources to differentiate between actual and theoretical concerns. We have a general learning module on using SPCs via the eMC here.

If you need to establish whether a drug is an inducer, inhibitor or substrate of **cytochrome p450**, then the Transformer website is comprehensive, although it is a technical/scientific resource, rather than a clinical one.

There are three valuable websites for interactions in therapeutic areas where regimens can be complex. They let you enter all the medicines involved and check for interactions:

- Cancer medicines
- HIV medicines
- Viral hepatitis medicines

The subscription sources **Martindale**, **AHFS Drug Information**, Lexicomp or Micromedex can be useful additional resources for interaction enquiries. If your enquiry involves an **alternative medicine**, then you may need to refer to some of the sources listed in that tutorial to help you.

Be careful about conducting a general internet search on this subject. 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...

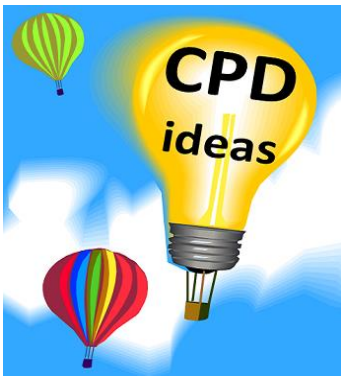
You may have questions about the role that cytochrome p450 enzymes play in drug metabolism. A review that may answer a number of these was published in Pharmacology & Therapeutics in 2013. This is a lengthy and complex scientific paper, not a clinical one. But if you are prepared to browse through it, you will find answers to questions like: Which isoenzymes are most important for drug clearance? Does gender or age affect enzyme activity? etc

Pharmacists are often asked about two potential outcomes of drug interactions that a wide range of medicines can cause. You may like to read more about these:

1. **Prolonged QT interval**. Here are two example online reviews that you may find helpful: Australian Prescriber (2015) and Therapeutic Advances in Drug Safety (2012). These are quite technical papers so you may prefer to browse them, rather than reading right through. There is also a helpful Drug and Therapeutics Bulletin on the topic if you have access.

2. **Serotonin syndrome**. The journal American Family Physician (2010) has a helpful review article that may assist you.

Continuing professional development



Here are some CPD activities ideas for you to consider:

★ Have you ever found it difficult to talk to a doctor about an interaction? If so, reflect on why this was the case. How might you do it better next time?
★ Write up an account of an interaction that you managed in practice and present it as a case study at your work journal club, or as part of your diploma. Highlight how your intervention had an impact on patient care.
★ Sit down with a pharmacist colleague to discuss an interaction that you prevented or managed on your ward. Did your colleague agree with your approach? What did you learn from sharing your experiences?
★ Are there any aspects of this topic that make you feel uncertain, or where you know you need a better understanding? If so, then find a relevant review to read, and write up what you learn as a CPD exercise.