UPDATE
Clinical
Module 1742

This module covers:

- The incidence of drug interactions in the UK
- Types of interaction, their effect on the metabolism and elimination of drugs from the body
- Interactions of high-risk medicines
- How community pharmacists can help prevent adverse effects of drug interactions

March

Clinical: Alternative remedies and interactions month

CAM regulations	March 7*
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**Online-only for Update Plus subscribers*

Common drug interactions

Sarah McBride

Today's NHS faces great pressures from an increasingly elderly population with multiple health conditions and high levels of polypharmacy.

This means pharmacists are more likely than ever to come across drug interactions – the modulation of a drug's effect by prior or concomitant administration of another substance, causing the original drug to become more or less potent.

Interactions exist between many commonly prescribed and non-prescription drugs, and are more likely to occur when multiple regular medicines are taken. Drug interactions can also be triggered by particular constituents of foods or alcohol.

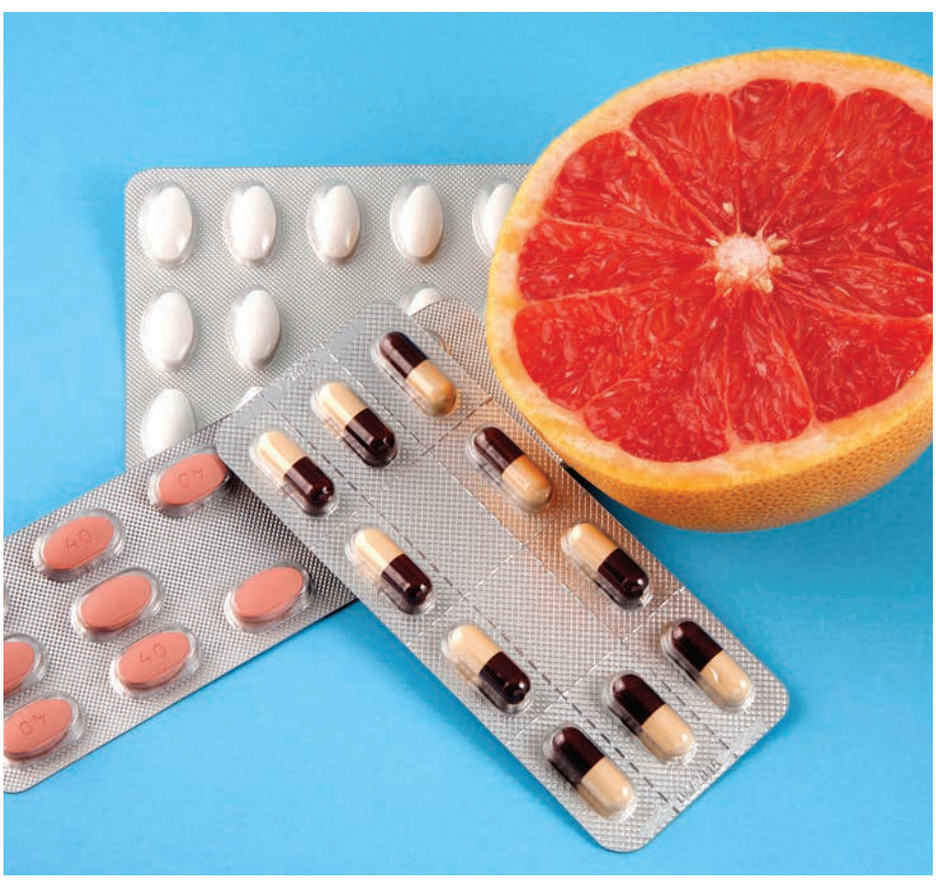
Adverse drug events occur when essential medicines become toxic or sub-therapeutic, leading to preventable patient harm.

These adverse drug events can not only result in poor health outcomes but also place an increased financial burden on the health system.

Medicine-related hospital admissions often involve high-risk drugs identified by PSNC for MURs and are considered to account for just over 4 per cent of patient admissions in the UK. In a recent study of emergency readmissions to an NHS hospital, drug interactions made up 7 per cent of medicine-related readmissions and were considered avoidable.

Many drug interactions are harmless and those that are potentially harmful only occur in a small proportion of patients; moreover, the severity of an interaction varies from one patient to another. Patients at increased risk from drug interactions include the elderly and those with impaired renal or liver function.

Generally, pharmacists can predict the effects of drug combinations through an understanding of the main mechanisms of interaction, which can be divided into two main types: pharmacokinetic or pharmacodynamic interactions.



Cytochrome p450 isozymes regulate first-pass metabolism of drugs and foods such as grapefruit juice

Pharmacokinetic interactions

Pharmacokinetic interactions can occur during the process of drug absorption, plasma protein binding, metabolism or elimination and are associated with changes in blood concentrations.

Drug absorption: Drugs can modify the absorption of others from the gastrointestinal (GI) tract – for example, vitamin C aids the absorption of iron when administered simultaneously. Food inhibits absorption of flucloxacillin, which therefore should be taken on an empty stomach to ensure the patient benefits from the full therapeutic effect.

Plasma protein binding: Certain drugs are strongly bound to plasma proteins and their potency depends on the concentration of the unbound drug. When co-administered, these drugs compete for binding sites and result in higher levels of unbound drugs, making them more potent.

Metabolism: The cytochrome P450 isozymes, including CYP2E1, CYP3A4, and CYP1A2, act principally in the liver and regulate first-pass metabolism of substrate drugs including warfarin, carbamazepine, erythromycin, amiodarone, theophylline, substances such as grapefruit juice and cigarette smoke. Certain drugs also induce or inhibit particular CYP450

enzymes, resulting in modified metabolism of the substrate drug and decreased or increased blood drug concentrations.

Elimination: P-glycoprotein is an efflux transporter that pumps drugs back into the lumen of the GI tract, reducing their absorption. P-glycoprotein inducers such as rifampicin and inhibitors such as verapamil can reduce or increase the concentration of susceptible drugs. These include calcium channel blockers, dabigatran, digoxin, erythromycin and loperamide. Several drugs that are transported by P-glycoprotein are also metabolised by CYP3A4.

Pharmacodynamic interactions

Pharmacodynamic interactions occur when drugs act at the same or interrelated receptor sites, resulting in additive, synergistic or antagonistic effects of each drug at the target receptor. For example, taking tramadol and selective serotonin reuptake inhibitors (SSRIs) together can create an excess of serotonin at the receptor, known as serotonin syndrome, which is potentially life-threatening.

High-risk medicine interactions

The following high-risk medicines are commonly known to cause drug interactions:

Non-steroidal antinflammatory drugs

Non-steroidal antinflammatory drugs (NSAIDs) including diclofenac, naproxen, ketoprofen and ibuprofen inhibit the generation of prostaglandins by blocking the cyclooxygenase enzymes Cox-1 and Cox-2.

Prostaglandins are mediators of inflammation and pain, but also have important roles in gastroprotection and maintenance of kidney blood flow. They also contribute to platelet stickiness and vascular function.

Therefore, NSAIDs increase the risk of bleeding when used with anticoagulant and antiplatelet drugs. Patients should look out for signs of bleeding, ie unexplained bruising, nosebleeds, blood in stools or coffee ground vomit.

NSAIDs should not be used routinely in combination with low-dose aspirin because there is an increased risk of GI disturbances including discomfort, nausea, diarrhoea, and ulceration/bleeding. To avoid these effects, low-dose aspirin and NSAID administration should be separated by approximately two hours. SSRIs such as citalopram should also be used with caution because they can impair platelet function and increase risk of bleeding when coprescribed with NSAIDs.

Systemic as well as local effects of NSAIDs contribute to GI disturbances. Preventative measures such as co-administration of a proton pump inhibitor (PPI), taking the drug with food or changing the route of administration may only partially reduce symptoms. Among NSAIDs, ibuprofen has the lowest risk profile for GI bleeding and is considered safe when used at the lowest effective dose for the shortest period necessary. Cox-2 selective inhibitors such as celecoxib are associated with a lower risk of GI bleeding. Patients experiencing adverse GI symptoms should be told to stop taking the NSAID and inform their doctor.

Care should also be taken with methotrexate, which is commonly prescribed as an antirheumatic drug in rheumatoid arthritis. When co-administered with NSAIDs, renal elimination of methotrexate can be reduced and cause toxicity. NSAIDs are not contraindicated with low-dose methotrexate, but patients should report symptoms of sore throat, dyspnoea or cough to their doctor and routine monitoring (full blood count, renal and liver function tests) should be undertaken more frequently.

NSAIDs can cause renal impairment (especially in older patients), sodium and water retention and can antagonise the actions of antihypertensive drugs including angiotensin-converting enzyme (ACE) inhibitors and diuretics.

Anticoagulants

Anticoagulants increase the risk of bleeding – especially when used in combination with antiplatelets, NSAIDs or SSRIs. Common anticoagulants include enoxaparin, tinzaparin, warfarin – a vitamin K antagonist – and the increasing popular oral drugs such as dabigatran, apixaban and rivaroxaban.

Warfarin is a widely used anticoagulant metabolised by CYP3A4, CYP1A2 and CYP2D6 enzymes and has many known interactions. Patients should be advised to avoid grapefruit juice, which is a strong inhibitor of CYP3A4. Warfarin binds strongly to plasma proteins and levels can be altered by drugs such as phenytoin.

Alcohol can markedly change levels of warfarin in the blood and therefore patients should drink alcohol in moderation according to national guidelines. The pharmacological actions of warfarin are antagonised by foods containing vitamin K, such as green leafy vegetables. Drastic changes in consumption of these foods should be avoided in order to ensure a stable international normalised ratio (INR). ▶

The Yellow Card Scheme

The MHRA collects information from healthcare professionals and patients on suspected problems involving adverse drug reactions (ADRs), including those from drug interactions, using the Yellow Card Scheme (mhra.gov.uk/yellowcard).

All ADRs that are serious, medically significant and result in harm should be reported and also those associated with newer black triangle medicines because there is less data supporting their safety profile. The MHRA will take action, if necessary, to minimise risk and maximise benefit to patients, often by means of drug safety updates.

Low-dose aspirin and NSAID administration should be separated by approximately two hours.

It is important the patient is counselled thoroughly on potential interactions and signs of bleeding and has their INR tested at regular intervals.

Dabigatran, rivaroxaban and apixaban are becoming favoured options for anticoagulation because they do not require regular blood monitoring. However, some interactions also exist for this group. Rivaroxaban is metabolised by CYP3A4 and levels are affected by inducers or inhibitors of this enzyme. The absorption of rivaroxaban is increased by co-administration with food; taking the drug on an empty stomach reduces its efficacy.

Dabigatran is a substrate for P-glycoprotein and its levels can be reduced by drugs which induce or inhibit this transporter.

Antiplatelet medicines

Antiplatelet medicines including aspirin, clopidogrel, prasugrel and dipyridamole are indicated for primary and secondary prevention of coronary events. They should not be used in combination with anticoagulants or NSAIDs because this increases the risk of bleeding. Taking clopidogrel together with omeprazole or esomeprazole is discouraged because this combination is thought to promote the metabolism of clopidogrel, reducing its levels. Alternative PPIs such as lansoprazole are a preferred treatment option.

Diuretics

Diuretics including loop diuretics, potassium-sparing diuretics and aldosterone antagonists are prescribed as an adjunct in hypertension and to reduce oedema in heart failure. The combined use of diuretics and drugs that cause hypotension, eg angiotensin II receptor antagonists such as candesartan and alpha blockers such as doxazosin, can give rise to additive hypotensive effects. This is especially important to note in the case of elderly patients, as it puts them at an increased risk of falls.

Diuretics are often used safely with ACE inhibitors; however the combination can result in first-dose hypotension, causing dizziness and light-headedness. The combination of these drugs can induce renal impairment in patients with or without existing renovascular disease.

Loop diuretics can cause hypokalaemia when combined with drugs that are also potassium-depleting - such as theophylline, corticosteroids and some laxatives. This increases the potential for torsade de pointes (a distinctive polymorphic ventricular tachycardia) with any drug that prolongs the QT interval.

In contrast, potassium-sparing diuretics such as amiloride can contribute to hyperkalaemia when combined with ACE inhibitors and angiotensin II receptor antagonists.

Respiratory drugs

Theophylline is a narrow therapeutic index drug metabolised by CYP1A2 and used as a bronchodilator in the treatment of asthma. Theophylline levels can be affected by co-administration of CYP1A2 inducers/inhibitors such as ciprofloxacin, carbamazepine and polycyclic hydrocarbons in cigarette smoke. Symptoms of theophylline toxicity include vomiting, agitation, restlessness, dilated pupils, sinus tachycardia and hyperglycaemia.

Patients who want to stop smoking should be informed that their dose of theophylline may require reduction after cessation. It takes about one week for the effect of the induction of CYP1A2 to wear off and dose adjustment is not usually necessary for temporary smoking cessation (eg during an acute hospital stay).

Non-cardioselective beta blockers such as propranolol should be used with caution in patients with asthma. They oppose the bronchodilator effects of beta-agonist bronchodilators such as salbutamol and higher doses may be required to reverse bronchospasm. Cardioselective beta blockers such as atenolol can sometimes cause acute bronchospasm in patients with asthma, but do not generally inhibit the bronchodilator effect of beta-agonist bronchodilators.

The role of the pharmacist

The pharmacist is in a prime position to advise and support patients in managing their medicines through MURs. Patients commonly use over-the-counter (OTC) medicines and see different prescribers for various conditions. This could mean that their GP is not aware of all the medicines a patient is taking and could prescribe an interacting medicine.

It should be clearly explained to all patients that some of their prescribed medicines may interfere with OTC medicines or their diet: herbal medicines, supplements, alcohol and even certain foods. These may make their medicines harmful, or prevent them from working as they could cause side effects.

Pharmacists can help minimise the risk of adverse drug events by:

- reconciling a patient's current medicines, including OTC treatments, supplements, alcohol and vitamins, particularly after transition between care settings
- reviewing medications for potential pharmacokinetic and/or pharmacodynamic drug interactions
- monitoring for adverse effects and advising patients on actions to be taken if affected
- recommending alternative medicines with a lower risk of interaction to prescribers
- promoting self-care by educating the patient on the safe use of non-prescription drugs, nutritional supplements, as well as potential drug-food interactions
- suggesting everyday tips to help avoid interactions, such as keeping a list of interacting foods in the kitchen, or using reminder charts or labels for medicine boxes to ensure correct administration of medicines taken at different times of the day
- encouraging patients to ask their pharmacist or doctor before taking any new medicines and to discuss any issues they may have with their current regimen.

Online resources for patients

- NHS Choices: nhs.uk
- Patient information: patient.co.uk
- Patient information leaflets: xpil.medicines.org.uk
- Yellow Card Scheme: yellowcard.mhra.gov.uk

Sarah McBride is a locum pharmacist based in London

Looking for tips to get the most out of your MURs? Try C+D's popular MUR Zone

chemistanddruggist.co.uk/mur-zone

5 minute test

■ Sign up to take the 5 Minute Test and get your answers marked online: chemistanddruggist.co.uk/update

Take the 5 Minute Test

1. The cytochrome P450 isozymes regulate the first-pass metabolism of warfarin, carbamazepine and erythromycin.
True or false?

2. P-glycoprotein inducers such as verapamil increase the concentration of susceptible drugs such as digoxin and loperamide.
True or false?

3. Tramadol and SSRIs can cause serotonin syndrome if taken together.
True or false?

4. NSAIDs inhibit the generation of prostaglandins by blocking the Cox-1 and Cox-2 enzymes.
True or false?

5. Naproxen has the lowest risk profile for gastrointestinal bleeding.
True or false?

6. Low-dose aspirin and NSAID administration should be separated by approximately two hours.
True or false?

7. Omeprazole is preferred over lansoprazole and esomeprazole if a PPI is required in patients taking clopidogrel.
True or false?

8. Loop diuretics can cause hypokalaemia when combined with other potassium-depleting drugs.
True or false?

9. Theophylline levels can be affected by co-administration of ciprofloxacin, carbamazepine and polycyclic hydrocarbons in cigarette smoke.
True or false?

10. Cardioselective beta blockers should not be used in asthma patients because they inhibit beta-agonist bronchodilators.
True or false?

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Tips for your CPD entry on common drug interactions

Reflect **How do pharmacokinetic and pharmacodynamic drug interactions differ? Drastic changes in the consumption of which foods should patients taking warfarin avoid? Which drugs can interact with diuretics?**

Plan **This article discusses common drug interactions and the role of the pharmacist in preventing them. It includes information about pharmacokinetic and pharmacodynamic interactions and the drugs with a high risk of interactions such as NSAIDs, anticoagulants, antiplatelet drugs, diuretics and respiratory drugs.**

Act **Read the Update article and the suggested reading (below), then take the 5 Minute Test (above). Update and Update Plus subscribers can then access answers and a pre-filled CPD logsheet at chemistanddruggist.co.uk/mycpd.**

Read more about how food and drugs interact on the Food and Drugs Interactions website
tinyurl.com/interactions11

Find out more about smoking and drug interactions from the Mersey Care NHS Trust Medicines Information Centre leaflet
tinyurl.com/interactions12

Find out more about the Yellow Card Scheme on the MHRA website
tinyurl.com/interactions13

Identify any patients who might benefit from an MUR and consult the C+D MUR Zone for information about specific drugs
tinyurl.com/interactions14

Evaluate **Are you now confident in your knowledge of commonly occurring drug interactions? Could you spot at-risk patients and advise on preventing adverse reactions?**

EXPERT Q&A

Want to know more? Our expert is on hand to answer any further questions you may have on this month's topic. Email queries to: **asktheexpert@updateplus.co.uk**