# Drug interactions

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## Abstract

Drug–drug interactions (DDIs) arise when the effects of one drug are altered by the co-administration of another. The clinical response depends on many factors, including individual patient characteristics such as age, co-morbidities and pharmacogenetics. The number of potential DDIs is extensive, but the incidence in published studies implies that many of these are not clinically relevant. Interactions are classified as pharmacokinetics-related, where drug absorption, distribution, metabolism or excretion is affected, or pharmacodynamics-related, when drugs with similar pharmacological actions are co-prescribed. The mechanism underlying drug interactions are now better understood, notably those involving the family of cytochrome P450 isoenzymes, as well as those related to P-glycoprotein and organic anion transporter polypeptides, which act as drug transporters in the liver and kidneys. These molecules exhibit genetic polymorphisms that influence the likelihood of clinically relevant DDIs following drug co-administration. With an ageing population, an increasing number of new drugs and more polypharmacy, increasing efforts are needed to avoid DDIs. Although computerized programs can reduce the number of DDIs, a risk–benefit evaluation by the prescribing physician is also required. This article outlines the main mechanisms involved in clinically relevant DDIs.

**Keywords** Cytochrome P450; drug interactions; P-glycoprotein; pharmacodynamics; pharmacokinetics; polypharmacy

## Key points

- Drug–drug interactions (DDIs) account for around a sixth of all adverse reactions to drugs
- Many potential DDIs are involved, although only a small proportion are relevant in clinical practice
- Pharmacokinetic interactions occur when one drug alters the handling of another by altering its absorption, distribution, metabolism or excretion
- Pharmacodynamic interactions occur when two drugs act on the same drug target (e.g. cell surface receptor, enzyme) or physiological system (e.g. blood clotting, blood pressure, central nervous system, plasma electrolyte concentration)
- DDIs can be minimized if prescribers are aware of them (especially when prescribing high-risk drugs), avoid polypharmacy where possible, use appropriate reference resources, monitor drug therapy appropriately, take advice from clinical pharmacists and use decision support systems where available

## Introduction

Drug–drug interactions (DDIs) represent a significant problem for prescribers and, with ever more drugs available and guidelines recommending multiple drug therapies for common conditions, the potential for interactions increases. Many theoretical DDIs are not clinically relevant as they do not result in a clinically significant adverse outcome (see Table 1 for classification by severity). Although some adverse drug reactions, such as first-dose anaphylaxis, can be unpredictable, DDIs can often be identified and prevented. Clinically relevant adverse outcomes are more likely if DDIs involve drugs with a low therapeutic index and patients who are more vulnerable because of age or disease (e.g. renal impairment). With an ageing population, more polypharmacy and an increase in the number of people taking alternative therapies, there is an increasing potential for drug interactions. Therefore, there is a growing need for clinical vigilance, surveillance and reporting of adverse reactions to the relevant drug safety authorities.

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## Frequency of drug interactions

The number of potential DDIs far outweighs the number of adverse reactions related to them that are actually encountered in clinical practice. The proportion of clinically relevant DDIs ranges from 3% to 20% and is related to the number of drugs taken by the patient. In a large prospective study of 18,820 patients, 6.5% of hospital admissions were related to an adverse drug reaction, of which one in six was caused by a DDI. In a recent analysis of community prescribing in Scotland between 1995 and 2010, the proportion of adults prescribed ten or more medications tripled, while the proportion of potentially serious DDIs more than doubled.[1] These figures are likely to increase without preventive measures including prescriber education and clinical decision support tools.

### Classification of drug interactions by severity

A life-threatening or contraindicated combination
Dosage adjustment or close monitoring is needed
Give guidance about possible adverse effects and/or consider some monitoring
No interaction, or no interaction of clinical significance

Source: Stockley's Drug Interactions, 11th ed. Claire Preston (Ed.) London: Pharmaceutical Press; 2011.

**Table 1**

New approaches to identifying DDIs involving translational bioinformatics are under investigation.[2] These novel methods involve computational techniques such as data-mining of adverse reaction databases and text-mining of medical records, online literature repositories and internet search logs to identify data signals. Results of interest can then be further examined using more traditional methods. These approaches should identify a large proportion of adverse events caused by DDIs that are currently unknown, missed or unreported. Common examples of DDIs are shown in Table 2.

## Principal mechanisms underlying drug interactions

There are three mechanisms by which drugs interact with each other.

### Pharmaceutical interactions

These are uncommon and occur when drugs are mixed inappropriately in syringes or infusion fluids before administration (e.g. phenytoin precipitates if mixed with a glucose solution before administration). Most DDIs are related to altered pharmacokinetics and/or pharmacodynamics.

### Pharmacokinetic interactions

These account for most commonly encountered DDIs and occur when one drug affects the absorption, distribution, metabolism or excretion of another. This results in an increased or decreased exposure to one or other drug. Most involve impaired drug elimination because of interference with hepatic metabolism, renal excretion or transcellular transport.

**Absorption:** although altered stomach acidity or binding of a drug to another substance in the stomach can affect drug absorption, most drug absorption interactions occur in the small intestine, because of a change in intestinal blood flow or intestinal motility, or an alteration in the bacteria that reside in the intestine. Common examples include the following:

- metoclopramide increases stomach emptying and the rate of delivery of co-administered drugs (e.g. ciclosporin, modified-release theophylline) to the small intestine
- colestyramine and other binding agents can impair the bioavailability of other drugs (e.g. furosemide), and ferrous sulphate can chelate levothyroxine.

**Distribution:** alterations in blood flow caused by, for example, reduced cardiac output or vasoconstriction can affect drug distribution. Many medications bind extensively to plasma proteins such as albumin in the bloodstream and can be prevented from reaching their site of action. However, a drug bound in this way can be displaced from its binding site by another with greater binding affinity, increasing the amount of (unbound) drug available to cause an effect. For example, diazepam displaces phenytoin from plasma proteins, resulting in an increased plasma concentration of unbound phenytoin and an increased risk of adverse effects. The effects of protein displacement are usually of limited clinical significance as the metabolism of the affected drug usually increases in parallel with the increased concentration of unbound drug, so that any effects of the interaction are normally short-lived.

**Hepatic metabolism:** DDIs related to hepatic metabolism are common. This is because many drugs are broken down by specific microsomal isoenzymes of cytochrome P450 (CYP). CYP3A4 is responsible for most DDIs, and its activity can vary by >50-fold in the general population. These enzymes are subject to relatively specific induction or inhibition by other drugs; examples of common substrates and their inducers and inhibitors are shown in Table 3.

The metabolism of a substrate drug can be altered by a second, interacting drug. The interacting drug can induce the formation of new isoenzymes, leading to increased activity of that pathway and metabolism of the substrate drug. This in turn reduces the plasma concentration and activity of the substrate drug. For example, the plasma concentration of novel oral anticoagulants (NOACs) apixaban, dabigatran and rivaroxaban is reduced by 50% when co-administered with carbamezapine, phenytoin or rifampicin, increasing the risk of thromboembolism.

Alternatively, the activity of cytochrome enzymes can be inhibited, reducing the elimination of the substrate drug and increasing its activity, with resulting exaggerated effects. For example, terfenadine, a non-sedating antihistamine, is metabolized by CYP3A4 to fexofenadine. Ketoconazole inhibits the metabolism of terfenadine, leading to its accumulation and the blockage of potassium channels in the heart, with consequent QT prolongation and potentially fatal arrhythmia known as torsade de pointes. Another common CYP3A4 interaction is inhibition by macrolide

### Drug interactions commonly leading to hospital admission

| Drug combination | Adverse event |
|---|---|
| Warfarin and aspirin | GI bleeding |
| NSAIDs and aspirin | GI adverse effects |
| Warfarin and interacting drugs | Bleeding (GI and non-GI) |
| Diuretic combinations | Renal failure |
| Diuretics and ACE inhibitors | Renal failure |
| Digoxin and interacting drugs | Digoxin toxicity |

ACE, angiotensin-converting enzyme; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug.

**Table 2**

**Examples of substrates of different CYP isoenzymes, with inducers and inhibitors of their metabolism**

| Substrates | Inducers | Inhibitors |
|---|---|---|
| **CYP1A2** | | |
| Clozapine, propranolol, theophylline | Carbamazepine, phenytoin, rifampicin, tobacco smoking | Cimetidine, ciprofloxacin, erythromycin |
| **CYP2C9** | | |
| Aspirin and most NSAIDs, diazepam, (*S*)-warfarin | Carbamazepine, phenobarbital, phenytoin, rifampicin | Amiodarone, cranberry juice, fluvoxamine (other SSRIs are weak inhibitors), metronidazole, omeprazole, ritonavir, tolbutamide |
| **CYP2D6** | | |
| β-Blockers (several), codeine, flecainide, phenothiazine, propafenone, TCAs | | Amiodarone, chlorphenamine, fluoxetine, haloperidol, ketoconazole, paroxetine, phenothiazines, quinidine, ritonavir, sertraline, TCAs, venlafaxine |
| **CYP3A4** | | |
| Apixaban, atorvastatin, calcium channel blockers, ciclosporin, cisapride, codeine, felodipine, midazolam, OCs, rivaroxaban, sildenafil, simvastatin, terfenadine, triazolam, verapamil, (*R*)-warfarin | Barbiturates, carbamazepine, dexamethasone, ethosuximide, phenytoin, rifabutin, rifampicin, St John's wort | Amiodarone, calcium channel blockers (especially diltiazem), clarithromycin, ciclosporin, cimetidine, danazol, erythromycin, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, itraconazole, indinavir, lansoprazole, ketoconazole, metronidazole, norfloxacin, omeprazole, quinine, ritonavir, saquinavir, sertraline, tacrolimus, tamoxifen, TCAs, venlafaxine, voriconazole, zafirlukast |

NSAIDs, non-steroidal anti-inflammatory drugs; OCs, oral contraceptives; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Adapted from Feely J, Barry M. Adverse drug interactions. *Clin Med* 2005; **5**(1); 19—22.

**Table 3**

antibiotics (e.g. clarithromycin) causing increased exposure to hydroxymethylglutaryl co-enzyme A reductase inhibitors (e.g. simvastatin) and a risk of myopathy or rhabdomyolysis.

DDIs involving metabolism have the opposite effect if the substrate drug depends on cytochrome P450 isoenzymes for transformation into its active form. Interacting drugs that induce metabolism increase the pharmacological actions of the substrate drug, while those that inhibit isoenzymes reduce pharmacological activity. For example, CYP2D6 metabolizes the pro-drug codeine into morphine, which is required for its opioid activity, and drugs that inhibit CYP2D6 reduce the analgesic response. Conversely, CYP3A4 inducers such as carbamazepine increase the risk of bleeding with the antiplatelet agents clopidogrel and prasugrel, by increasing the rate of metabolism of these pro-drugs to active compounds.

The likelihood that these metabolism related DDIs lead to significant adverse effects is related to the steepness of the dose—response curve of the substrate drug and the dosage of the interacting drug. Most interactions resulting from inhibition of metabolism occur relatively early after taking the combination of drugs, and the effects of inhibition are usually short-lived once the inhibitor has been withdrawn. However, where there is irreversible binding of an enzyme system, as with monoamine oxidase inhibitors, it can take several weeks for the effect to dissipate and for new enzyme to form. By contrast, drug interactions caused by enzyme induction require new enzyme formation, so the onset of effect is more gradual and may not be maximal for 1—2 weeks. The half-life of the inducing drug influences the speed of metabolism, drugs with a shorter half-life (e.g. rifampicin) inducing metabolism more quickly than those with longer half-lives because they reach a steady-state concentration more rapidly. Similarly, the effect of enzyme induction can take a week or more to dissipate when the inducer is withdrawn. It is important to note that stopping an interacting medication can also cause an adverse effect. For example, an increase in warfarin's anticoagulant effect can occur when stopping enzyme-inducing antiepileptics such as carbamazepine or when a patient stops smoking (another inducer of enzyme activity). Mutual induction and inhibition can also occur. For instance, dose adjustment may be required when antiepileptic drugs are used in combination because of mutual induction and inhibition of the CYP3A4 isoenzyme.

**Elimination:** a relatively small reduction in renal elimination can result in a disproportionate increase in drug exposure and toxicity, especially in patients with a reduced glomerular filtration rate (GFR), such as elderly individuals. This is most likely for drugs that are predominantly renally excreted and have a low therapeutic index (e.g. digoxin, lithium, aminoglycosides). Drug interactions involving renal mechanisms primarily involve

interference with excretion by alteration of the GFR or competition for a common tubular transport system:

- aminoglycoside antibiotics can reduce GFR, particularly if trough concentrations are elevated, leading to accumulation of the aminoglycoside itself as well as a number of other drugs that depend on renal excretion (e.g. digoxin)
- non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of methotrexate toxicity because of competition for renal tubular excretion.

***Transcellular transport*** – P-glycoprotein is a drug transporter protein that enables the transport of a variety of drug substrates across cell membranes. It is expressed at high levels in several normal tissues within organ systems that influence drug absorption (intestine), drug elimination (liver and kidney) and distribution to the site of action (central nervous system, haematological cells). The complexity of this system is becoming apparent with the recognition that it too exhibits genetic polymorphism and is subject to induction and inhibition interactions in a similar way to the CYP drug-metabolizing enzyme system, involving a similar range of inducers and inhibitors.

Table 4 lists some drugs that are substrates for P-glycoprotein, including some anticancer agents, antibiotics and antihistamines. If two or more of these substrate drugs are co-prescribed, they may compete for P-glycoprotein transport, leading to an alteration in their absorption, excretion and tissue distribution at sites where this protein is expressed. For example, clarithromycin inhibits P-glycoprotein, reducing the renal excretion of digoxin and resulting in higher plasma concentrations and an increased risk of digoxin toxicity. NOACs are substrates for CYP3A4 and P-glycoprotein, and are frequently prescribed for patients with atrial fibrillation who are also taking drugs such as verapamil, amiodarone and dronedarone, which are also P-glycoprotein substrates or inhibitors. To reduce the risk of bleeding, NOACs should either be co-prescribed in a lower dosage (e.g. dabigatran and verapamil) or avoided altogether (e.g. rivaroxaban and dronedarone).[3]

### Pharmacodynamic interactions

Pharmacodynamic interactions occur when co-prescribed drugs act on the same target or physiological system. They can be a particular problem in elderly patients and those taking drugs affecting the central nervous system. These interactions can lead to synergism (when two or more drugs with similar pharmacodynamic effects are given) or antagonism (when drugs with opposing pharmacodynamic effects are given). At the receptor level, one drug can have a greater efficacy than another, and if these drugs are co-prescribed the action of the more efficacious drug may be antagonized (e.g. the partial opioid agonist buprenorphine antagonizing the effects of the full agonist morphine). Drugs that have actions on the same system by acting on different targets can also interact (e.g. NSAIDs, aspirin and anticoagulants can interact to cause gastrointestinal haemorrhage).

Central nervous system depressants (e.g. benzodiazepines, 'Z' drugs) can interact to cause falls and hip fracture, especially among elderly people.[4] Other common pharmacodynamic interactions include:

- α-adrenergic antagonists prescribed for benign prostatic hyperplasia in men taking a calcium channel blocker for hypertension resulting in orthostatic hypotension and falls
- diuretics causing hypokalaemia and thereby increasing the effects of digoxin on the heart
- drugs that tend to increase potassium concentration (e.g. angiotensin-converting enzyme inhibitors, spironolactone, potassium supplements, trimethoprim) being co-prescribed and causing hyperkalaemia.

**P-glycoprotein substrates**

| | |
|---|---|
| Cardiac drugs | Digoxin, quinidine, losartan |
| Immunosuppressants | Ciclosporin, tacrolimus |
| Calcium channel blockers | Diltiazem, verapamil |
| Antihistamines | Terfenadine, cimetidine |
| Central nervous system drugs | Ondansetron, morphine, phenytoin |
| Anticancer drugs | Dactinomycin, etoposide, doxorubicin, vinblastine |
| Antibiotics | Erythromycin, rifampicin |
| HIV protease inhibitors | Indinavir, ritonavir |
| Anticoagulants | Dabigatran, apixaban, rivaroxaban, edoxaban |

**Table 4**

### Avoiding drug interactions

There are a number of ways in which prescribers can reduce the risk of DDIs:

- Most serious DDIs involving commonly prescribed drugs are predictable, so a combination of awareness of DDIs and appropriate use of good reference resources (e.g. the *British National Formulary*) helps when prescribing.
- Polypharmacy is a major cause of increased DDI risk and is common because of the expanding indications for drug therapy and an ageing population with multimorbidity. Prescribers should be aware that guidelines do not always consider the wider impact of polypharmacy and the potential for DDIs among those with multiple co-morbidities,[5] and must take responsibility for assessing the risks for individual patients. Careful consideration when using high-risk drugs, in tandem with the avoidance of both polypharmacy and frequent changes in drug prescriptions, will help to minimize DDIs. Prescribing tools such as the STOPP/START criteria, the updated Beers criteria and the FORTA list are useful when prescribing common medications in the elderly.
- Medication reconciliation, review and de-prescribing can further reduce the risk of drug interactions. It is important to avoid a 'prescribing cascade'. This occurs when a patient complains of symptoms suggestive of a side-effect of their current pharmacotherapy. The patient is then prescribed another medication to counter this effect rather than undergoing a trial of stopping the offending medication.
- Comprehensive drug histories are vital and should include non-prescribed drugs such as over-the-counter

medications, herbal therapies and recreational drugs, which may be involved in DDIs.

- Plasma drug monitoring of high-risk drugs, such as those with a low therapeutic index, helps to detect an increased concentration before it causes toxicity, or a decreased concentration before it leads to therapeutic failure.
- In future, pharmacogenetics may help to guide individual dosing regimens in patients following the identification of gene mutations that are involved in the metabolism of the drugs and increase the risk of DDI's.
- Clinical pharmacists will be highly experienced at spotting potential DDIs but it will remain the responsibility of prescribers to decide whether the risk justifies avoiding or stopping drug treatment.
- Electronic prescribing coupled with decision support tools can help to alert prescribers to potential interactions, although these must focus on moderate- or high-probability interactions to avoid alert fatigue.
- Careful reporting of all adverse reactions that are suspected of being related to a DDI will be important in alerting the regulatory authorities and the wider medical community to DDIs, which are unlikely to be discovered in drug development because of the selected nature of the trial participants. ◆

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