Adverse drug reactions and interactions

Gurpreet S Jutley

Mark Pucci

Robin E Ferner

Jamie J Coleman

Abstract

Adverse drug reactions (ADRs) remain a challenge in modern healthcare, particularly given the increasing complexity of therapeutics, an ageing population and rising multimorbidity. These factors also influence the number of drugs taken on average by patients. Prescribers should be aware of the potential for the drug–drug interactions (DDIs) that commonly arise in clinical practice. This article summarizes some of the key facts about ADRs and DDIs and explores aspects relating to their prevention, diagnosis and management in clinical practice.

Keywords Adverse drug reaction reporting systems; adverse drug reactions; clinical pharmacology; drug interactions; pharmacovigilance

Key points

- Adverse drug reactions (ADRs) — unintended, harmful events caused by medicines — contribute to or occur during many unscheduled hospital admissions
- A careful medication history can help prescribers to understand the patient's previous experiences with drug treatment, particularly in identifying previous ADRs that could preclude re-exposure to a drug
- Preventing ADRs depends on avoiding treatment in patients whose susceptibility is increased and using a therapeutic plan that reduces the risk of an adverse effect (e.g. avoiding the co-administration of other drugs, monitoring blood test results)
- Spontaneous reporting (e.g. the Yellow Card Scheme in the UK) based on the *suspicion* of an ADR is an important part of pharmacovigilance. Overall, ADRs are vastly underreported across healthcare settings and sectors; if in doubt, submit a report

Introduction

Medicines can have effects that differ from their intended therapeutic effect. A *side effect* is any effect caused by a drug other than the intended therapeutic effect, whether it be beneficial, neutral or harmful. When unintended effects are harmful, they are termed *adverse drug effects*. In common usage, however, side effect usually refers to undesirable or harmful effects. An *adverse drug reaction* (ADR) is 'a response to a medicinal product that is noxious and unintended'.[1]

Gurpreet S Jutley *MB ChB MRCP(UK) PhD is a Clinical Pharmacology Speciality Trainee at University Hospitals Birmingham NHS Foundation Trust, UK. Competing interests: none declared.*

Mark Pucci *BSc MSc PGDip MB ChB MRCP(UK) is a Consultant in Clinical Toxicology and Acute Medicine at University Hospitals Birmingham NHS Foundation Trust, UK. Competing interests: none declared.*

Robin E Ferner *MSc MD FRCP is Honorary Professor of Clinical Pharmacology at the Institute of Clinical Sciences, University of Birmingham and Honorary Clinical Professor in the Clinical Pharmacology Section, University College London, UK. Competing interests: REF is Emeritus Director of the West Midlands Centre for Adverse Drug Reactions, Birmingham, UK, and has provided expert advice to Coroners and others on adverse drug reactions.*

Jamie J Coleman *MD MA FRCP is Honorary Professor of Clinical Pharmacology and Medical Education, Institute of Clinical Sciences, University of Birmingham and Consultant Physician, University Hospitals Birmingham NHS Foundation Trust, UK. Competing interests: JJC is a member of the Commission of Human Medicines and Chair of the Pharmacovigilance Expert Advisory Group of the Medicines and Healthcare Products Regulatory Agency (MHRA) and Director of the West Midlands Centre for Adverse Drug Reactions, Birmingham, UK, which receives funding through the Yellow Card Centre from the MHRA.*

ADRs can be difficult to diagnose as they can be mistaken for symptoms of the condition being treated or confused with other natural diseases, and often simply go unrecognized. ADRs range from relatively minor symptoms to life-altering events; the more serious ADRs are often associated with hospital admission, prolonged hospital stay, excessive morbidity, increased treatment costs and occasionally death.

It has proved difficult to estimate the burden of ADRs because of underdiagnosis and underreporting. In Europe, the proportion of acute hospital admissions caused by ADRs in 17 studies varied from 0.5% to 12.8%, and the percentage of patients who developed an ADR during a hospital admission ranged from 1.7% to 50.9%.[2]

A recent prospective analysis of all medical admissions to a UK teaching hospital found that a prevalence of 18.4% of patient admissions were associated with an ADR, of which the authors classified 40.4% as avoidable or possibly avoidable.[3] The mortality rate arising from an ADR was 0.34% of all admissions. Patients with an ADR had longer hospital stays, and, when projected nationally, the annual cost to the health service in England was £2.21 billion.

Classification of adverse drug reactions

ADRs have traditionally been classified into two types:

- type A reactions — sometimes referred to as augmented reactions — which are predictable on the basis of the pharmacology of the drug
- B reactions—bizarre reactions — which are not predictable on the basis of the pharmacology.

Although still widely quoted, this basic classification does not distinguish between ADRs with very different clinical presentations, such as those with chronic adverse effects associated with cumulative drug exposure (e.g. osteoporosis with long-term corticosteroid treatment) or withdrawal reactions (e.g. rebound

Please cite this article as: Jutley Gurpreet S et al., Adverse drug reactions and interactions, Medicine, https://doi.org/10.1016/j.mpmed.2023.10.006

hypertension after cessation of centrally acting antihypertensives). An alternative classification considers Dose-relatedness, Time course and Susceptibility (DoTS).[4]

Dose-relatedness

All pharmacological effects are dose related. Some ADRs occur in susceptible individuals at doses far below the therapeutic range on the dose–response curve (Figure 1). These are termed *hypersusceptibility* reactions. Examples includes immunoglobulin E-mediated (anaphylactic) and non-immunoglobulin-mediated (anaphylactoid) activation of mast cells and basophils that can result in an acute, sometimes fatal, multisystem syndrome.

Toxic effects can occur if the dose is too high, when drug elimination is reduced or as a result of interaction with other drugs. Intercurrent illness can also trigger toxic reactions. For example, hypokalaemia induced by acute gastroenteritis can provoke digitalis (digoxin) toxicity.

Collateral ADRs occur at standard therapeutic doses.

Time course

Many ADRs depend not only on the concentration of the drug at the site of action, but also on the duration and frequency of its presence there. The toxicity of methotrexate, for example, is greater when a lower dose is repeatedly administered than when the same amount is given as a single dose. ADRs from corticosteroids are predominantly associated with treatment over weeks and months, or with very high doses. ADRs can be either time independent or time dependent.

Time-independent reactions – some reactions can occur at any time during treatment and are independent of the duration of the course. For example, the risk of bleeding with warfarin depends on the degree of anticoagulation, not the duration of treatment.

Time-dependent reactions – the time from administration to the occurrence of an adverse reaction can be characteristic. For example, *anaphylactic reactions* occur shortly after exposure to the first dose of a course of the causative agent.

Delayed-type hypersensitivity reactions often occur between 10 days and 10 weeks after starting a drug (e.g. toxic epidermal necrolysis in response to carbamazepine). Drug-induced Cushing syndrome caused by chronic treatment with corticosteroids provides an example of an ADR that occurs only after weeks or months of treatment.

Delayed reactions can occur long after a course of treatment is over, and are exemplified by the substantially increased rate of second cancers in patients treated with alkylating agents many years before.

Susceptibility

The risk of an ADR can follow a normal distribution within an exposed population, or can vary with age, renal function, physiological state or other factors that can affect the pharmacokinetics or pharmacodynamics of a drug. The risk can also be confined to a small group of patients who are susceptible to rare ADRs because of genetic differences that alter the handling of a drug or the physiological response to it. For instance, prolonged apnoea can occur after standard doses of succinylcholine in patients with mutations in the gene coding for pseudocholinesterase (butyrylcholinesterase), which then fails to metabolize succinylcholine.

Pharmacogenetic variation (i.e. drug–gene interactions) in relation to ADRs is increasingly seen as a way to predict and therefore prevent susceptible individuals being given drugs that put them at high risk of ADRs. Patients with the mitochondrial mutation m.1555A > G (in *MT-RNR1*), for example, are at greatly increased risk of deafness from gentamicin and should where possible be treated with other agents. In the USA, many drug

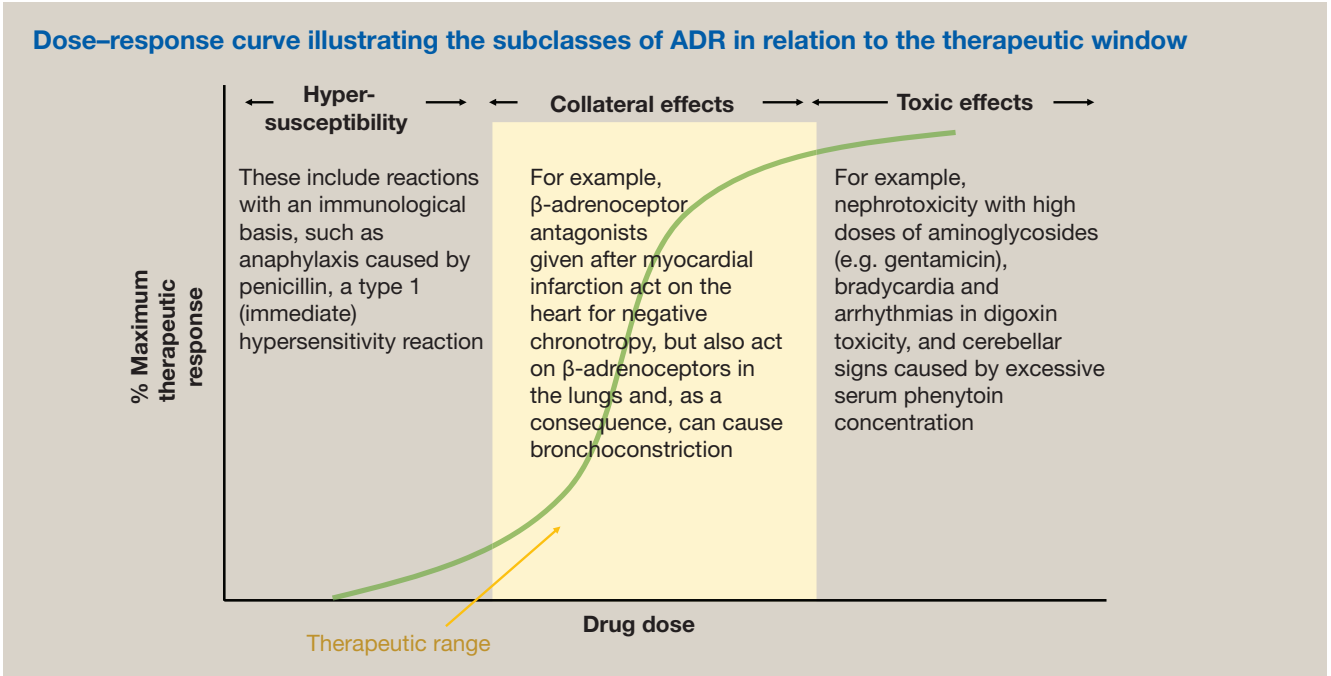


Figure 1

Please cite this article as: Jutley Gurpreet S et al., Adverse drug reactions and interactions, Medicine, https://doi.org/10.1016/j.mpmed.2023.10.006

labels (i.e. details of prescribing information) provide data on drug–gene interactions to support appropriate dosing or avoidance to improve therapy and reduce the risk of harm.[5]

Ethnicity can also be important. For example, patients described as Black are three times more likely than 'non-Black' patients to develop angioedema with angiotensin-converting enzyme (ACE) inhibitors. Other factors that influence susceptibility to ADRs include age, sex, pregnancy status, concomitant disease, other co-administered drugs and diet.

Some common and important syndromes induced by drugs, together with putative biological mechanisms, are illustrated in Table 1.

Abnormal drug metabolism: changes that alter the rate of metabolism of a drug also alter the amount present at the site of action, and thereby the extent and duration of the beneficial and adverse effects. The most important enzymes responsible for drug metabolism are the hepatic microsomal oxidases (cytochrome P450 system), of which CYP2D6 and CYP3A4 are especially relevant.

The *CYP2D6* gene is highly polymorphic. The 'poor metabolizer' phenotype is present in about 9% of the population in the UK, about 1% of Arabic people and 30% of the Hong Kong Chinese population. Poor metabolizers eliminate substrates of CYP2D6 more slowly than normal. These substrates include metoprolol, paroxetine, haloperidol, amitriptyline, flecainide and tamoxifen. Conversely, there are ultra-rapid metabolizers who are more likely to experience adverse effects from codeine (methyl-morphine, a pro-drug) as it is more completely and rapidly converted into active morphine by the aberrant enzyme.

CYP3A4 is the major enzyme responsible for the metabolism of, for example, alprazolam, carbamazepine, ciclosporin, quetiapine and tacrolimus. The uncommon *CYP3A4*22* gene variant is associated with reduced metabolism of ciclosporin and tacrolimus. The antiplatelet drug clopidogrel is a pro-drug and requires conversion to the active metabolite by CYP2C19. 'Clopidogrel resistance' is therefore more common in patients who are CYP2C19 poor metabolizers.

Detection and diagnosis

When harm occurs during or after drug treatment, it may have been caused the drug but could also be a manifestation of the disease for which the drug was being taken, or it may have another cause. In the simplest case, the reaction is identified by its close relationship in time to drug, exposure, its resolution when the drug is stopped (de-challenge) and sometimes, its emergence when the drug is restarted (re-challenge). However, this clear relationship seldom occurs in practice. Some reactions (e.g. teratogenesis and neurodevelopmental disorders in offspring from *in utero* drug exposure) only become evident long after exposure. Some (including fatal reactions) are irreversible, and some occur only when several factors coincide and do not recur at re-challenge.

It is helpful to know whether the event is likely to be a manifestation with the underlying disease, whether it has previously been reported with the drug in question, and if not, whether it might be predicted from what is known of the drug's structure and mode of action. Causality assessment tools (e.g. Naranjo algorithm, Liverpool Adverse Drug Reaction Causality Assessment Tool) are useful to study associations in research environments, but less useful in assessing individual patients.

ADRs may not be discovered during clinical trials, which are primarily designed to establish efficacy and gain regulatory approval. For example, rare reactions may not be observed, and an increase in the incidence of relatively frequent adverse events can be missed. The detection of ADRs depends heavily on spontaneous reporting systems (e.g. UK Yellow Card scheme), stimulated post-marketing surveillance (e.g. Drug Safety Research Unit's Modified Prescription-Event Monitoring scheme), specific proactive schemes (e.g. Vaccine Monitoring platform) and case–control studies of the proportion of individuals exposed and not exposed to the drug in groups with and without the condition. Increasingly large data sets, or so called 'big data', can support the pharmacoepidemiological investigation and discovery of ADRs.

For an ADR report to spontaneous reporting schemes to be valid only four items of information are required: an identifiable patient, a reaction, a suspected medicinal product, and an identifiable reporter. Reporters are, however, encouraged to provide as much information as possible to provide additional data and clinical context for assessors. Unfortunately, underreporting remains a key challenge: probably <5% of all ADRs are reported in practice. The UK Yellow Card scheme has been strengthened by the introduction of direct reporting by patients, public awareness since the coronavirus vaccine introduction, online access (https://yellowcard.mhra.gov.uk/) and a smartphone app.

Preventing adverse drug reactions

While some ADRs are unpredictable – such as anaphylaxis in a patient after their first exposure to a penicillin-containing antibiotic – many are preventable with adequate foresight and monitoring. Interventions that reduce the probability of an ADR occurring are important to reduce the risk of patient harm. There are two basic steps that can be followed to reduce risk:

- identify the subgroup of patients who are likely to be susceptible to the adverse effect and modify the treatment choice accordingly
- ensure that the treatment plan mitigates any possible adverse effects.

An appreciation of the mechanism of action and relevant susceptibilities (Table 1) can help to prevent ADRs (e.g. drug–gene interactions).

Prudent, safe prescribing is key to reducing errors that can contribute to ADRs. Treatment plans should consider possible adverse effects and seek to reduce their risk and mitigate their effects should they occur. For example, co-prescribing folic acid with methotrexate reduces the incidence of adverse effects associated with folate deficiency; initiating treatment with an ACE inhibitor in controlled conditions can avoid the consequences of first-dose hypotension; and biochemical monitoring can prevent electrolyte disturbance and renal impairment during diuretic treatment.

Importantly, adopting a patient-centred approach during a consultation, listening to a patient's previous experiences with drugs, appreciating the person's understanding of risk and coming to a mutual decision about drug therapy is key in clinical

Please cite this article as: Jutley Gurpreet S et al., Adverse drug reactions and interactions, Medicine, https://doi.org/10.1016/j.mpmed.2023.10.006

Some common and important ADRs

Drug-induced disorder	Examples of causative drugs	Mechanism
Oxidative haemolysis	Primaquine, dapsone, the sulfamethoxazole component of co-trimoxazole	Oxidizing agents can cause potentially fatal haemolysis in individuals with poorly functioning glucose 6-phosphate dehydrogenase
Myopathy	Hydroxymethylglutaryl co-enzyme A reductase inhibitors ('statins') including simvastatin and atorvastatin	Individuals homozygous for a single-nucleotide polymorphism in a region coding for a liver-specific organic anion transporter (solute carrier organic anion transporter 1B1 (SLCO1B1)) have a greater uptake of statin into muscle and much increased risk of myopathy
Stevens–Johnson syndrome/toxic epidermal necrosis	Abacavir, allopurinol, carbamazepine	This serious cutaneous ADR has been associated with various human leukocyte antigen genotypes (e.g. abacavir and HLA B*57:01; carbamazepine and HLA B*15:02 in Han Chinese individuals)
Acute toxic confusion	On drug withdrawal: barbiturates, benzodiazepine, ethanol, γ-hydroxybutyrate, 'Z' drugs (zolpidem, zopiclone) On drug administration: anticholinergics such as oxybutynin, antiparkinsonian agents, cannabis, corticosteroids, digoxin, H_2-antagonists, opioids, stimulant drugs	The risk of drug-induced acute toxic confusion is increased in elderly individuals who already have cognitive impairment and in patients with hepatic encephalopathy
Progressive multifocal leukoencephalopathy	Natalizumab, alemtuzumab	The antibodies allow reactivation of John Cunningham (JC) virus in the central nervous system, which causes a degenerative brain disease
Bronchoconstriction	β-adrenoreceptor antagonists NSAIDs	NSAIDs induce bronchoconstriction in about 10% of patients with asthma; the risk is increased if they also have nasal polyps
Interstitial lung disease	Nitrofurantoin, bleomycin, busulfan	The immune damage to the lung may be due to drug-specific antibodies or drug-specific T cells
Peptic ulcer disease	NSAIDs	Cyclooxygenase-1 inhibition diminishes prostaglandin secretion and reduces its cytoprotective effects in gastric mucosa
Torsade de pointes	Many drugs that prolong the QT interval, including: antiarrhythmics — amiodarone, disopyramide and sotalol; antibacterial agents — erythromycin, moxifloxacin; citalopram; methadone; antipsychotics such as haloperidol	This broad-complex tachycardia in which the QRS axis changes sinusoidally from 0° to 180° is caused by problems with repolarization of the cardiac myocyte. It is often drug induced and is more common in women and in patients with hypomagnesaemia or hypokalaemia
Venous thromboembolism	Anti-androgens, oestrogen-containing contraceptives, anti-TNF therapy	A variant gene coding for factor V Leiden increases the risk in heterozygous, and much more in homozygous, women
Bone marrow suppression	Clozapine, carbimazole, carbamazepine	

Please cite this article as: Jutley Gurpreet S et al., Adverse drug reactions and interactions, Medicine, https://doi.org/10.1016/j.mpmed.2023.10.006

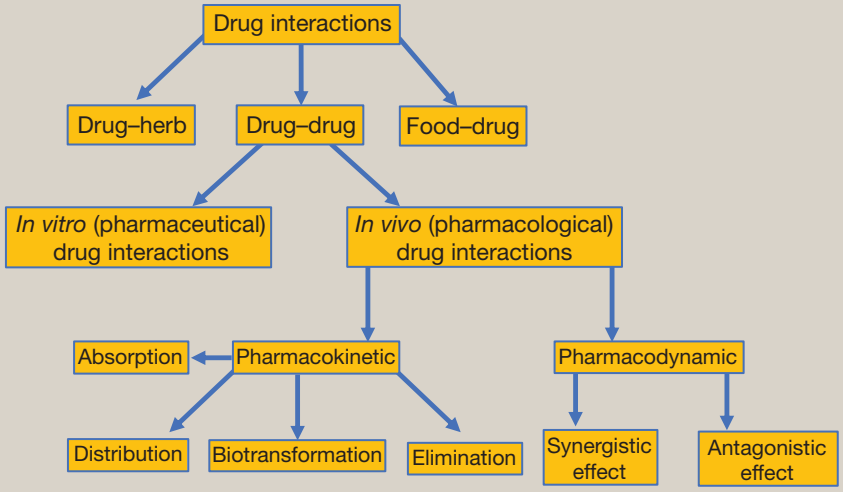
		The myelosuppression is immune mediated; patients can present with mouth ulcers, sepsis with agranulocytosis, petechiae or haemorrhage
Methaemoglobinaemia	Local anaesthetics, dapsone, amyl and isobutyl nitrite ('poppers')	These drugs oxidize Fe^{2+} in haem to Fe^{3+}, which shifts the oxygen dissociation curve to the left
Abnormal glucose metabolism	Pentamidine, thiazide diuretics, glucocorticoids	Pentamidine is toxic to pancreatic β-cells Thiazides inhibit insulin secretion Glucocorticoids inhibit post-receptor signalling and thus cause insulin resistance
Ketoacidosis	SGLT2 inhibitors: canagliflozin, dapagliflozin	Glycosuria caused by SGLT2 inhibition decreases plasma glucose concentration and reduces insulin release. Carbohydrate deficit, insulinopenia and increased glucagon release then increase lipolysis and ketogenesis, but blood glucose concentrations can be normal
Osteonecrosis of the jaw	Bisphosphonates	Impaired remodelling of bone can occur after dental procedures such as extraction or implant placement
Serotonin syndrome	SSRIs, linezolid, tramadol	The is caused by excessive serotonin; the risk is greatest when several mechanisms operate: reduced serotonin metabolism (monoamine oxidase inhibitors), increased serotonin release (ecstasy), reuptake inhibition (SSRIs)
Neuroleptic malignant syndrome	Haloperidol, chlorpromazine, olanzapine	Dopamine D_2 receptor antagonism results in rigidity and extrapyramidal signs in addition to disturbance of cognition and autonomic function over days to weeks of taking the offending drug
Immune-related ADRs (e.g. gastrointestinal — pancreatitis, enterocolitis; respiratory — pneumonitis; endocrine — thyroiditis)	Immune checkpoint inhibitors: nivolumab, pembrolizumab, atezolizumab	Immune-related ADRs usually develop in weeks to months after treatment initiation as a result of T cell activation against healthy tissue as well as tumour cells, cytokine production and complement-mediated inflammation

NSAID, non-steroidal anti-inflammatory drugs; SGLT2, sodium-glucose co-transporter 2; SSRI, selective serotonin reuptake inhibitor; TNF, tumour necrosis factor.

Table 1

Please cite this article as: Jutley Gurpreet S et al., Adverse drug reactions and interactions, Medicine, https://doi.org/10.1016/j.mpmed.2023.10.006

Categories of drug interaction



Drug–drug interactions can be further arranged into:
(A) *In vitro* (pharmaceutical) drug interactions (occurring outside the body)
(B) *In vivo* (pharmacological) drug interactions (occurring inside the body):
(a) pharmacokinetic interactions: those interfering with: (1) absorption, (2) distribution, (3) biotransformation, (4) elimination
(b) pharmacodynamic interactions: those producing: (1) additive or synergistic effects, (2) antagonistic effects

Figure 2

Effects of several food–drug and drug–herb reactions

Food–drug interactions

Food	Drug or drug class	Reaction
Any	Rifampicin, iron, penicillin	Food reduces absorption
Milk products	Tetracyclines, fluroquinolones, sulfonamides	Calcium chelates with these drugs and reduces absorption
Foods containing tyrosine or tryptophan (cheese, especially blue cheese; wine)	Monoamine oxidase inhibitors (tranylcypromine)	Tyrosine accumulates and releases noradrenaline (norepinephrine), which precipitates hypertensive/hyperadrenergic crises
Leafy vegetables	Warfarin	High vitamin K intake can diminish the effect of vitamin K antagonism

Drug–herb interactions

Herb	Drug or drug class	Reaction
Various herbs	Warfarin	Increases effect: ginkgo, denshen (Chinese sage), garlic (inhibits platelet aggregation), ginger (anticoagulant activity) Decreased effect: green tea (a source of vitamin K), St John's wort (metabolism increased)
St John's wort	Various drugs	Induces microsomal enzymes and can increase the metabolism of various drugs including antidepressants, antiretrovirals, ciclosporin and warfarin
Black cohosh	Antihypertensives	Antihypertensive effects are diminished

Table 2

Please cite this article as: Jutley Gurpreet S et al., Adverse drug reactions and interactions, Medicine, https://doi.org/10.1016/j.mpmed.2023.10.006

practice. Sharing information about the risk of ADRs, discussing potential premonitory features and instituting a suitable monitoring scheme can mitigate any harms that might occur.

Drug–drug and drug–food interactions

When two or more medications are administered concurrently, or a medicine is taken with certain food or drink, interactions can result in unintended effects, toxicity or a lack of clinical efficacy. Drug interactions are common, especially in high-risk groups such as elderly patients, who have a high burden of polypharmacy and poor physiological reserve. Figure 2 shows a classification of drug interactions. Table 2 outlines the effects of several food–drug and drug–herb reactions.

Drug interactions can affect each of the four aspects of pharmacokinetics – absorption, distribution, metabolism and elimination. For example, the absorption of iron from ferrous salts can be inhibited by co-administration with tetracycline; clarithromycin can inhibit the metabolism of warfarin and increase the risk of bleeding; and methotrexate excretion can be inhibited by competition with non-steroidal anti-inflammatory drugs.

Drugs can have opposing or complementary pharmacodynamic actions, and complementary actions can be additive or synergistic. ◆

KEY REFERENCES

1 Ferner RE, McGettigan P. Adverse drug reactions. *BMJ* 2018; **363:** k4051.

2 Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. *Drug Saf* 2015; **38:** 437–53.

3 Osanlou R, Walker L, Hughes DA, et al. Adverse drug reactions, multimorbidity and polypharmacy: a prospective analysis of 1 month of medical admissions. *BMJ Open* 2022; **12**: e055551.

4 Aronson JK. Meyler's side effects of drugs: the international encyclopedia of adverse drug reactions and interactions. Amsterdam: Elsevier, 2015.

5 Chang WC, Tanoshima R, Ross CJD, et al. Challenges and opportunities in implementing pharmacogenetic testing in clinical settings. *Annu Rev Pharmacol Toxicol* 2021; **61:** 65–84.

Acknowledgements

The views expressed in this publication are those of the authors alone and not necessarily those of the organizations with which they are affiliated.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 68-year-old man presented with crushing central chest pain and was found to have an anterior non-ST elevation myocardial infarction (NSTEMI). One week previously he had had a similar episode treated with stent insertion in the left anterior descending coronary artery. On this second occasion he was found to have a stent thrombosis. He had a history of type 2 diabetes, hypertension, and gastro-oesophageal reflux disease. He was of Chinese ethnic origin. On the second admission he was taking atorvastatin 40 mg once at night, bisoprolol 5 mg once daily, clopidogrel 75 mg once daily, lansoprazole 15 mg once daily, linagliptin 5 mg once daily, metformin 500 mg three times daily, ramipril 7.5 mg once daily, glyceryl trinitrate sublingual as required.

What is the mostly likely pharmacological reason for this second episode?

A. Cardiac myositis induced by atorvastatin
B. Clopidogrel resistance due to pharmacogenomic variation
C. Drug–drug interaction between the proton pump inhibitor and clopidogrel
D. Non-adherence to secondary preventative medication
E. Thrombocytosis caused by ramipril

Question 2

A 54-year-old man developed a sudden onset of right-sided weakness and unintelligible speech 4 days after starting treatment for community-acquired pneumonia. He had a history of prosthetic mitral valve replacement and was taking oral warfarin dosed daily according to international normalized ratio (INR) (target INR 3.5; time in therapeutic range 83%). He was of Caucasian background. He was taking oral antibiotics (amoxicillin and clarithromycin) and amlodipine for hypertension.

Investigations

- Full Blood Count:
  - Haemoglobin 128 g/litre (130–175)
  - White cell count 11.2 x 10^9/litre (3.0–10.0)
  - Neutrophils 8.3 x 10^9/litre (1.5–7.0)
  - Platelets 132 x 10^9/litre (150–400)
- Clotting:
  - INR 8.2 (<1.4)
- CT brain scan: acute intracerebral bleed in the left cerebrum

What is the mostly likely cause of this clinical picture?

A. Absorption disturbance of warfarin due to antibiotics
B. Metabolic drug–drug interaction between clarithromycin and warfarin
C. Non-adherence of warfarin during acute illness
D. Sepsis from partially treated pneumonia leading to disseminated intravascular coagulation
E. Thrombocytopenia secondary to amoxicillin therapy

Please cite this article as: Jutley Gurpreet S et al., Adverse drug reactions and interactions, Medicine, https://doi.org/10.1016/j.mpmed.2023.10.006

Question 3

A 58-year-old woman was admitted with fever and vomiting. She had a history of type 2 diabetes mellitus, hypertension and mild renal impairment treated with metformin, empagliflozin and ramipril. She was of Asian background. On admission she appeared dehydrated and was pyrexial (temperature 38.2°C). There was some mild abdominal tenderness on palpation. Her capillary blood glucose measurement was 12 mmol/litre.

Investigations

- Venous blood gas:
  - pH of 7.21 (7.35–7.45)
  - Bicarbonate 14 mmol/litre (21–29)
  - Lactate 2.7 mmol/litre (0.5–1.6)
  - Ketones 4.8 mmol/litre (<0.6)

What is the mostly likely cause of this clinical picture?

A. Hyperglycaemic ketoacidosis
B. Ketoacidosis due to a sodium-glucose co-transporter 2 inhibitor
C. Kidney injury due to an angiotensin-converting enzyme inhibitor
D. Lactic acidosis due to a biguanide
E. Metabolic acidosis due to septicaemia

Please cite this article as: Jutley Gurpreet S et al., Adverse drug reactions and interactions, Medicine, https://doi.org/10.1016/j.mpmed.2023.10.006